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Diiodomethyl p-tolyl sulfone (DIMTS) or Amical 48
Preliminary Work Plan
Registration Review: Initial Docket
Case Number 4009

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TERMS, ABBREVIATIONS AND SYMBOLS

AD	Antimicrobials Division
A.I. or a.i.	active ingredient
aPAD	acute population adjusted dose
ASRI	activated sludge respiration inhibition
atm-m^3/mole	atmospheric pressure-cubic meter per mole
BCF	bioconcentration factor
°C	degrees Celsius
CAS	Chemical Abstracts Service
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CMA	Chemical Manufacturers Association
CO_2	carbon dioxide
COC	concentration-of-concern
cPAD	chronic population adjusted dose
DCI	data call-in
DOC	Dissolved organic carbon
EC_{50}	median (or 50 percent) effect concentration
EC_{05}	5 percent effect concentration
ECOTOX	ECOTOXicology
EDI	estimated daily intake
EDSP	Endocrine Disruptor Screening Program
E-FAST	Exposure and Fate Assessment Screening Tool
EPI Suite	Estimation Program Interface Suite
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
FFDCA	Federal Food, Drug, and Cosmetic Act
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FQPA	Food Quality Protection Act
FWP	Final Work Plan
g/mol	grams per mole
GLN	guideline number
HPV	high production volume
IDS	Incident Data System
Koc	organic carbon normalized soil-water partition coefficient
Kd	soil-water partition coefficient
Kow	octanol-water partition coefficient
LC_{50}	median (or 50 percent) lethal concentration
LD_{50}	median (or 50 percent) lethal dose
LOAEC	lowest-observed-adverse-effect-concentration
LOEC	lowest-observed-effect-concentration
LOAEL	lowest-observed-adverse-effect-level
Log K_{ow}	logarithm of the octanol-water partition coefficient
µg	microgram
ml/g	milliliter per gram
mg/kg	milligram per kilogram
mg/kg/day	milligram per kilogram per day
mg/L	milligram per liter
mm Hg	millimeter of mercury

MOE	margin of exposure
MRID	Master Record Identification Number
MRL	maximum residue limit
N/A	not applicable
nm	nanometers
NOAEC	no-observed-adverse-effect-concentration
NOAEL	no-observed-adverse-effect-level
OCSPP	Office of Chemical Safety and Pollution Prevention
OECD	Organization for Economic Co-operation and Development
OPP	Office of Pesticide Programs
PAD	population adjusted dose
PAI	pure active ingredient
PDM	Probabilistic Dilution Model
%	percent
PC Code	Pesticide Chemical Code
PCF	pounds per cubic foot
pH	power of hydrogen or power of the concentration of the hydrogen ion
PHED	Pesticide Handler's Exposure Data
PIS	primary irritation score
pKa	power of the acid dissociation constant or negative base-10 logarithm of the acid dissociation constant of a solution
ppb	parts per billion
ppm	parts per million
PWP	Preliminary Work Plan
QSAR	quantitative structure-activity relationship
RED	Reregistration Eligibility Decision
SAR	structure activity relationship
SF	safety factor
SSTS	Section Seven Tracking System
TEP	typical end-use product
TGAI	technical grade active ingredient
TMDL	total maximum daily loads
UF	uncertainty factor
UV/VIS	ultraviolet/visible light absorption
% w/w	percent weight per weight.
WP	wettable powder
WWTPs	wastewater treatment plants

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1 Introduction

This document is the United States Environmental Protection Agency's (USEPA, EPA or "the agency") Preliminary Work Plan (PWP) for Diiodomethyl p-tolyl sulfone (DIMTS), formerly referred to as Amical 48. The PWP document explains what EPA's Office of Pesticide Programs (OPP) knows about DIMTS, highlighting anticipated data and assessment needs, identifying the types of information that would be especially useful to the agency in conducting the review, and providing an anticipated timeline for completing the DIMTS review.

The registration review process was designed to include a public participation component to solicit input from interested stakeholders. The agency intends, by sharing this information in the docket, to inform the public of what it knows about DIMTS and what types of new data or other information would be helpful for the agency to receive as it moves toward a decision on DIMTS. The agency encourages all interested stakeholders to review the PWP and to provide comments and additional information that will help the agency's decision-making process for this chemical.

1.1 Statutory and Regulatory Authority

The Food Quality Protection Act (FQPA) of 1996 mandated a registration review program. All pesticides distributed or sold in the United States generally must be registered by the USEPA based on scientific data showing that they will not cause unreasonable risks to human health or the environment when used as directed on product labeling. The registration review program is intended to make sure that, as the ability to assess risk evolves and as policies and practices change, all registered pesticides continue to meet the statutory standard of no unreasonable adverse effects to human health or the environment. Changes in science, public policy, and pesticide use practices will occur over time. Through the registration review program, the agency periodically reevaluates pesticides to make sure that as change occurs, products in the marketplace can be used safely. Information on this program is provided at http://www2.epa.gov/pesticide-reevaluation.

The agency is implementing the registration review program pursuant to Section 3(g) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and will review each registered pesticide every 15 years to determine whether it continues to meet the FIFRA standard for registration. The regulations governing registration review begin at 40 CFR 155.40. The agency will consider benefits information and data as required by FIFRA. The public phase of registration review begins when the initial docket is opened for each case. The docket is the agency's opportunity to state what it knows about the pesticide and what additional risk analyses and data or information it believes are needed to make a registration review decision. After reviewing and responding to comments and data received in the docket during this initial comment period, the agency will develop and commit to a Final Work Plan (FWP) and anticipated schedule for the DIMTS case.

1.2 Case Overview

The docket for DIMTS (case 4009) has been established at http://www.regulations.gov in docket number EPA-HQ-OPP-2015-0264. Documents associated with this registration review can be

viewed in this docket. Tables 1-2 below summarize the issues relevant to this registration review case and the anticipated registration review schedule.

Table 1 – Summary of Anticipated Risk Assessments and Data Needs for Registration Review: DIMTS

Risk Assessment	Assessment Necessary to Support Registration Review	Date of Most Recent Assessment	Type of Assessment Required (New/Updated)	Data Anticipated as Needed (See Table 7 for details)
Dietary (food)	Yes	3/28/2008 (RED)	Updated	Toxicology and Residue Data (Table 7)
Dietary (drinking water)	Yes	N/A	New	Environmental Fate Data (Table 7)
Occupational Handler	Yes	3/28/2008	Updated	(Table 7)
Occupational Post-Application Exposure	No	3/28/2008	None	None
Residential Handler	Yes	3/28/2008	Updated	(Table 7)
Residential Post Application - Incidental Oral and Dermal	Yes	3/28/2008	Updated	(Table 7)
Residential Post Application - Inhalation	No	3/28/2008	None	None
Aggregate	Yes	3/28/2008	Updated	(Table 7)
Cumulative	No	3/28/2008	None	None
Tolerance Review	No	N/A	None	None
Ecological	Yes	11/1/2007	Updated	Leaching-adsorption-desorption and Ecotoxicity data

N/A = Not applicable
*** Table 1 is a summary of the anticipated risk assessments and data needs for Registration Review. For data called in through the post-Reregistration Eligibility Decision (RED) Data Call-In (DCI), see Table 8 of this PWP.**

Table 2 – Anticipated Registration Review Schedule

Anticipated Activity	Target Date*	Completion Date
Phase 1: Opening the Docket		
Open Docket and 60-Day Comment Period for Preliminary Work Plan	2015-09	2015-09
Close Public Comment Period	2015-11	2015-11
Phase 2: Case Development		
Issue Final Work Plan	2016-03	
Issue Data Call-In (DCI)	2017-03	
Receive Data to be Considered in Risk Assessment	2019-03	
Open 30-Day Public Comment Period for Preliminary Risk Assessment(s)	2020-09	
Close Public Comment Period	2020-10	

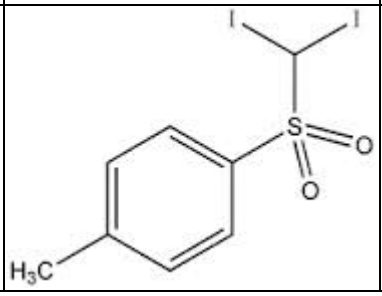
Phase 3: Registration Review Decision and Implementation		
Open 60-Day Public Comment Period for Proposed Decision	2021-03	
Close Public Comment Period	2021-05	
Issue Final Decision	2021-09	
Begin Post-Decision Follow-up	2021	
Total (years)	6	

*The anticipated schedule will be revised as necessary (*e.g.*, need arising under the Endocrine Disruptor Screening Program with respect to the active ingredients in this case).

1.3 Chemical Identification and Properties

Table 3 presents the active ingredient to be assessed in case 4009: DIMTS (PC Code 101002).

Table 3 – Chemical Identification of DIMTS

Chemical Name	DIMTS	Reference/Comments
PC Code	101002	N/A
CAS Number	20018-09-1	EPI-WEB 4.11
Smiles code	O=S(=O)(c(ccc(c1)C)c1)C(I)I	EPI-WEB 4.11
Molecular Formula	$C_8H_8I_2O_2S$	EPI-WEB 4.11
Molecular Weight (grams/mole)	422.02	EPI-WEB 4.11
Molecular Structure		N/A

The physical chemistry information for parent DIMTS relevant to risk assessment is summarized in Table 4, while the physical chemistry information for the degradates monoiodo-p-methyltolylsulfone (MIMPTS, parent compound minus one iodo group), methyl-p- tolylsulfone (MPTS, parent compound minus both iodo groups) and p-toluene sulfonic acid (PTSOA, parent compound minus both iodo groups and a methyl group with added hydroxyl group) are summarized in Table 5. Further information on physical chemistry is located in Appendix E.

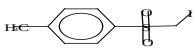
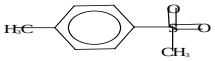
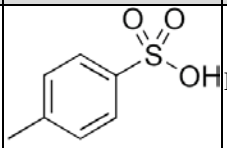
Table 4 – Physical-Chemical and Environmental Fate Properties for Parent DIMTS

Guideline No.	Parameter	DIMTS	Reference (MRID unless specified) Comments
830.7050	UV/Visible Absorption	Max sorption at 288 nm, some tailing through 409 nm	47234003
830.7370	Dissociation constant (pKa)	Not applicable	48511201

Guideline No.	Parameter	DIMTS	Reference (MRID unless specified) Comments
830.7550	Octanol-water partition coefficient at 25 °C (Log K_{ow})	2.66	42177202
830.7840	Solubility in water (mg/L)	<2	47373801
830.7950	Vapor pressure (mmHg)	4.9 x 10^{-7}	47373801
None	Henry's law constant at 25 °C (atm-m^3/mol)	1.4 x 10^{-7}	Calculated

atm-m^3/mol = atmosphere cubic meter per mole; °C = degrees Celsius; mg/L = milligrams per liter; mmHg = millimeters of mercury.

Table 5 – Physical-Chemical and Environmental Fate Properties for Monoiodo-p-methyltolylsulfone (MIMPTS), methyl-p- tolylsulfone (MPTS), and p-toluene sulfonic acid (PTSOA) Degradates

Guideline No.	Parameter	Monoiodo-p-methyltolylsulfone (MIMPTS)	Methyl-p-tolyl sulfone (MPTS)	P-toluene sulfonic acid (PTSOA)	Reference (MRID unless specified) Comments
None	Structure				None
None	Description	Parent minus 1 iodine	Parent minus two iodines	Hydroxylated, once-demethylated MPTS	None
None	PC Code	None	None	None	Not applicable
None	CAS No.	37891-96-6	59203-01-9	104-15-4	Dow MSDS (MIMPTS) Chemical Book (MPTS)
None	Smiles code	O=S(=O)(c(ccc(c1)C)c1)C(I)	O=S(=O)(c(ccc(c1)C)c1)C	O=S(O)(=O)(c(ccc(c1)C)c1)	EPI-WEB 4.11
None	Molecular formula	$C_8H_9IO_2S$	$C_8H_{10}O_2S$	$C_7H_8O_3S$	EPI-Web 4.11
None	Molecular weight	296.12	170.23	172.20	EPI-WEB 4.11
830.7050	UV/Visible Absorption	No data	No data	No data	Similar to parent
830.7370	Dissociation constant (pKa)	Not applicable	Not applicable	Not applicable	Similar to parent
830.7550	Octanol-water partition coefficient at 25 °C (Log K_{ow})	2.3	1.94	-0.62	47338402 (MIMPTS and MPTS) EPI-WEB 4.11 (PTSOA)
830.7840	Solubility in water (mg/L)	140.4	1,352	6.2 x 10^5	47338402 (MIMPTS and MPTS) EPI-WEB 4.11 (PTSOA)

Guideline No.	Parameter	Monoiodo-p-methyltolylsulfone (MIMPTS)	Methyl-p-tolyl sulfone (MPTS)	P-toluene sulfonic acid (PTSOA)	Reference (MRID unless specified) Comments
830.7950	Vapor pressure (mmHg)	2.3×10^{-5}	2×10^{-3}	2.9×10^{-6}	EPI-WEB 4.11
None	Henry's law constant at 25 °C (atm-m^3/mol)	6.4×10^{-8}	3.3×10^{-7}	1.1×10^{-12}	Calculated

atm-m^3/mol = atmosphere cubic meter per mole; °C = degrees Celsius; mg/L = milligrams per liter; mmHg = millimeters of mercury.

1.4 Use/Usage Description

1.4.1 Registrations

There are seven EPA-registered products that contain diiodomethyl p-tolyl sulfone as an active ingredient (a.i.). The percent a.i. ranges from 0.95 to 95 percent, and the formulations include flowable and soluble concentrates, liquids, and wettable powder. Some of these registered products also contain other active ingredients such as propiconazole, 3-iodo-propyl butyl carbamate (IDPC), and chlorothalonil.

1.4.2 Summary of Registered Uses

A summary of the registered uses of DIMTS that will be assessed in this registration review is shown in Table 6. DIMTS can be applied by the following application methods: roll coating, liquid pour, liquid pump, solid pour, solid place, sapstain spray and dip, airless sprayer (paints and stains), paint brush/roller (paints and stains) and high pressure sprayer (treated wood).

Table 6 – Summary of Diiodomethyl p-tolyl sulfone (DIMTS) Registered Uses

Uses	Application Method	Application Rate
Material Preservatives		
Paints	Liquid Pour	5700 ppm
	Liquid Pump	
	Roll Coating	
	Paintbrush/Roller	2850 ppm
	Airless Sprayer	
	Solid Pour	
	Solid Place	
Adhesives, caulks, dispersions, and sealants	Solid Pour	2358 ppm
	Solid Place	
	Liquid Pour	1650 ppm
	Liquid Pump	
Pigment Dispersions, Inks and Extender Slurries	Liquid Pour	1425 ppm
	Liquid Pump	

Uses	Application Method	Application Rate
Rubber, Plastics and Vinyl Products	Liquid Pour	7600 ppm
	Liquid Pump	7600 ppm
Paper Production	Liquid Pour	3156 ppm
	Liquid Pump	3156 ppm
	Solid Pour	3156 ppm
	Solid Place	3156 ppm
Hides and Leather	Liquid Pour	2650 ppm
	Liquid Pump	2650 ppm
	Solid Pour	3000 ppm
	Solid Place	3000 ppm
Textiles	Liquid Pour	5000 ppm
	Liquid Pump	5000 ppm
	Solid Pour	4750 ppm
	Solid Place	4750 ppm
Wood Preservatives		
Forest Products	Pressure Treatment	0.0065 lb ai/cu. ft
Forest Products	High Pressure Spray	400 ppm
Forest Products	Spray Sapstain	40 ppm
Forest Products	Dip	

1.5 Regulatory History

DIMTS was first registered as an active ingredient on September 17, 1980. A Reregistration Eligibility Decision (RED) was done in 2008. Currently, there are seven active registrations (EPA Reg. Nos. 464-670, 464-672, 464-673, 60061-112, 60061-126, 60061-127, and 74075-1) for products containing DIMTS as an algaecide, bactericide, and fungicide. It is used as a materials preservative in paints, air duct coatings, fire-retardant coatings, pigment dispersions, inks, emulsions, extender slurries, adhesives, caulks, sealants, rubbers, plastic, textiles, leather, paper production to protect pulp and slurries, paper/paperboard, and wetlap. It is also used as a wood preservative.

1.5.1 Recent/Pending Regulatory Actions

There are no recent or pending regulatory actions for DIMTS.

1.5.2 Tolerance Information

For DIMTS, there are no EPA registered direct food contact uses. However there are multiple registered labeled uses that could result in indirect food contact including under 21 CFR parts 175, 176 and 177: (1) use in caulks and sealants (adhesives), (2) use in rubber and plastic products (polymers), and (3) use as a mold preventer during paper production and paper storage

(paper slimicides). There is a Food and Drug Administration (FDA) food additive regulation under CFR 176.300, which allows 0.2 lb DIMTS per ton of dry weight fiber for paper and paper board. This food additive regulation in relation to currently registered uses for DIMTS is discussed further in Section 3.2.1 of this document.

EPA has not established tolerances or exemptions for tolerances in/on any raw agricultural commodities or processed food and feed products under the Federal Food, Drug and Cosmetic Act (FFDCA) Section 408.

1.6 Incidents

1.6.1 Human Health

No DIMTS human poisoning incidents have been reported in OPP's Incident Data System (IDS) since 1992 based on the search conducted on June 25, 2015.

1.6.2 Ecological

No DIMTS ecological incidents have been reported in IDS since 1992 based on the search conducted on June 23, 2015.

2 Anticipated Data Needs

Several studies were already required from the assessment of DIMTS in the 2008 RED. In addition to the already-required RED DCI data, the following studies as listed in Table 7 are anticipated to be needed for the registration review of DIMTS. Table 8 outlines the data requirements required by the post-RED DCI issued on February 24, 2010. The agency anticipates reviewing any data received in response to the post-RED DCI as well as data requested for this registration review prior to conducting the registration review risk assessments for DIMTS.

Table 7 – Studies Anticipated as Needed for the Registration Review of DIMTS

GLN	Study Name	Test Substance	Time Frame (Measured in months from DCI Receipt)	Risk Assessment(s) Data Will Support	Use Site(s) Triggering Anticipated Data Requirement	Applicable Exposure Scenario
835.1230	Leaching-adsorption-desorption	TGAI, MIMPTS, MPTS	12	Ecological	All	Ecological exposure and drinking water
850.1075	Acute estuarine/marine fish toxicity	TGAI	12	Ecological	All	Ecological exposure
850.1035	Mysid acute toxicity test	TGAI	12	Ecological	All	Ecological exposure
850.1025	Oyster acute toxicity test	TGAI	12	Ecological	All	Ecological exposure
850.1300	Aquatic invertebrate life cycle	MIMPTS	12	Ecological	All	Ecological exposure
850.1400	Fish early-life stage	MIMPTS	12	Ecological	All	Ecological exposure
850.3020	Honeybee acute contact	TGAI	12	Ecological	All	Ecological exposure
850.4400	Aquatic vascular plant growth	TEP	12	Ecological	All	Ecological exposure
850.4500	Aquatic plant growth (algal) [1]	TEP	12	Ecological	All	Ecological exposure
850.4550	Cyanobacteria toxicity [1]	TEP	12	Ecological	All	Ecological exposure
860.1340	Residue analytical method	TGAI	12	Human Health	All	Human health exposure
860.1380	Storage stability data	TGAI	12	Human Health	All	Human health exposure
870.4300	Combined Chronic Toxicity/Carcinogenicity	TGAI	24	Human Health	All	Human health exposure
870.6200	Neurotoxicity screening battery [2]	TGAI	24	Human Health	All	Human health exposure
870.7800	Immunotoxicity [3]	TGAI	12	Human Health	All	Human health exposure
None	Migration Study [4]	EP	12	Human Health	Paper production, plastics, adhesives and sealants	Human health exposure

[1]In a Federal Register Notice dated June 27, 2012, EPA split the Public Draft OPPTS 850.5400 test guideline into two test guidelines: OCSPP 850.4500 and OCSPP 850.4550. See "Final Test Guidelines; OCSPP 850 Series; Notice of Availability" 77 FR 38282, June 27, 2012. http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2009-0154-0028.

[2]Acute (study due 12 months after receipt of DCI) and subchronic (study due 24 months after receipt of DCI) neurotoxicity studies are anticipated to be required. A protocol should be submitted to the agency for review prior to conducting the neurotoxicity studies.

[3] All 90-day subchronic studies in the rodent can be designed to simultaneously fulfill the requirements of the 90-day immunotoxicity studies by adding separate groups of animals for testing of immunotoxicity parameters.

[4] Based on the results of the screening-level dietary (food) analysis for paper mold inhibition, paper plant storage and preservation, and food-contact polymers using label-provided inputs resulting in risks above the agency's level of concern for some population subgroups, the migration study is expected to be required and protocols must be approved by the agency prior to the initiation of the study.

Table 8 – Data Needs Required by the February 24, 2010 Data Call-In for the DIMTS RED

GLN	Study Name	Status
875.1100	Dermal exposure--outdoor	Study not received
875.1300	Inhalation exposure- outdoor	
875.1600	Application exposure monitoring data reporting	Waived
875.2300	Indoor Surface Residue Dissipation	Study not received
875.1700	Product Use	Acceptable
875.2700	Product Use	
875.2800	Description of Product Use	

3 Human Health Risk Assessment

The agency anticipates the need to conduct a human health risk assessment for DIMTS. The agency will evaluate the additional data required by the post-RED DCI. Additionally, the agency anticipates the need to require additional data for the registration review of DIMTS, based on the currently registered uses. These additional studies include mammalian toxicity data from a combined chronic toxicity/carcinogenicity study, an immunotoxicity study and neurotoxicity screening battery, and all applicable exposure studies. A detailed description of the available toxicity studies is provided in Appendix A.

3.1 Existing Toxicological Endpoints

The agency anticipates the need to revise the existing toxicological endpoints from the 2008 RED, shown in Table 9, as part of registration review. All available information, including existing toxicology studies and valid scientific literature, will be considered in establishing the toxicology endpoints to be used in the registration review risk assessment.

Table 9 – Existing Toxicological Endpoints for DIMTS

Exposure Scenario	Dose Used in Risk Assessment (mg/kg/day)	Target MOE, UF, Special FQPA SF, for Risk Assessment	Study and Toxicological Effects
Dietary Risk Assessments			
Acute Dietary (All populations)	No appropriate endpoint can be selected for acute RfD.		
Chronic Dietary (All populations)	NOAEL = 2	UF = 1000 (10x for inter-species extrapolation, 10x for intra-species variation, and 10x for lack of chronic and cancer data)	90-Day Oral Toxicity Study in Dogs (MRIDs 42054403 & 43246402) LOAEL = 2 mg/kg/day, based on histopathologic changes in the thyroid glands (degeneration [mineralization within colloid clumping of sloughed follicular cells and colloid depletion]) in the mid- and high-dose males and females, salivary gland (sialadenitis [ducted and periductal inflammation]) and gastrointestinal (GI) tract (hemorrhagic gastritis, necrosis).
	cRfD = 0.002 mg/kg/day		
Non-Dietary Risk Assessments			
Incidental Oral Short-Term (1-30days)	$NOAEL_{maternal}$ = 4	UF = 100 (10x for inter-species extrapolation, 10x for intra-species variation)	Developmental Toxicity in Rabbits (MRIDs 42243801/43246404) LOAEL = 15 mg/kg/day, based on clinical signs, reduced body weight gain and food consumption.

Exposure Scenario	Dose Used in Risk Assessment (mg/kg/day)	Target MOE, UF, Special FQPA SF, for Risk Assessment	Study and Toxicological Effects
Incidental Oral Intermediate-Term (1-6 months)	NOAEL = 2	UF = 100 (10x for inter-species extrapolation, 10x for intra-species variation)	90-Day Oral Toxicity Study in Dogs (MRIDs 42054403/43246402) LOAEL = 10 mg/kg/day, based on histopathological changes observed in the thyroid glands (degeneration of the thyroid gland [mineralization within colloid clumping of sloughed follicular cells and colloid depletion]), salivary gland (Sialadenitis [ductal and periductal inflammation of the salivary gland]) and gastrointestinal (GI) tract (hemorrhagic gastritis, necrosis of the small intestine and keratitis).
Dermal Absorption Factor	12% (based on a pharmacokinetics and metabolism study in rats (MRID 47076641)		
Dermal Short-Term (1-30 days)	$NOAEL_{maternal}$ = 4	UF = 100 (10x for inter-species extrapolation, 10x for intra-species variation)	Developmental Toxicity in Rabbits (MRIDs 42243801/43246404) LOAEL = 15 mg/kg/day, based on clinical signs, reduced body weight gain and food consumption.
Dermal Intermediate-Term (1-6 months)	NOAEL = 2	MOE = 100 (10x for inter-species extrapolation, 10x for intra-species variation)	90-Day Oral Toxicity Study in Dogs (MRIDs 42054403/43246402) LOAEL = 10 mg/kg/day, based on histopathological changes observed in the thyroid glands (degeneration of the thyroid gland [mineralization within colloid clumping of sloughed follicular cells and colloid depletion]), salivary gland (Sialadenitis [ductal and periductal inflammation of the salivary gland]) and gastrointestinal (GI) tract (hemorrhagic gastritis, necrosis of the small intestine and keratitis).

Exposure Scenario	Dose Used in Risk Assessment (mg/kg/day)	Target MOE, UF, Special FQPA SF, for Risk Assessment	Study and Toxicological Effects
Dermal Long-Term (> 6 months)	NOAEL = 2	MOE = 1000 (10x for inter-species extrapolation, 10x for intra-species variation, 10x for lack of chronic and cancer and reproductive data)	90-Day Oral Toxicity Study in Dogs (MRIDs 42054403/43246402) LOAEL = 10 mg/kg/day, based on histopathological changes observed in the thyroid glands (degeneration of the thyroid gland [mineralization within colloid clumping of sloughed follicular cells and colloid depletion]), salivary gland (Sialadenitis [ductal and periductal inflammation of the salivary gland]) and gastrointestinal (GI) tract (hemorrhagic gastritis, necrosis of the small intestine and keratitis).
Inhalation (All Durations)	NOAEL = 2	MOE = 1000 (10x for inter-species extrapolation, 10x for intra-species variation, 10x for route-to-route extrapolation)	90-Day Oral Toxicity Study in Dogs (MRIDs 42054403 & 43246402) LOAEL = 10 mg/kg/day, based on histopathological changes observed in the thyroid glands (degeneration of the thyroid gland [mineralization within colloid clumping of sloughed follicular cells and colloid depletion]), salivary gland (Sialadenitis [ductal and periductal inflammation of the salivary gland]) and gastrointestinal (GI) tract (hemorrhagic gastritis, necrosis of the small intestine and keratitis).
Cancer (oral, dermal, inhalation)	No carcinogenicity data available for DIMTS. This study is anticipated to be required.		

3.2 Dietary Exposure

The agency anticipates the need to conduct a dietary exposure (food and drinking water) assessment to support registration review of DIMTS since there are multiple labeled uses that could result in indirect food contact and the potential for entering surface water and, therefore, dietary exposure (food and drinking water) to DIMTS.

3.2.1 Food

The agency anticipates the need to conduct dietary (food) exposure assessments as part of the registration review process to update the previously conducted dietary (food) exposure assessments in the 2008 RED. There are multiple labeled uses that could result in indirect food contact, and, therefore, dietary exposure to DIMTS. The registered uses of DIMTS (EPA Reg. Nos. 464-670, 464-672, and 464-673) that may result in dietary exposure include: (1) use in

caulks and sealants, (2) use in rubber and plastic products, and (3) use as a mold preventer during paper production and paper storage.

Currently, the label statement on EPA Reg. No. 464-670 reads "This product is not cleared for use in the manufacture of paper and paperboard products that come in contact with food." However, this registrant indicated they plan to submit a label change amendment and other information in order to allow food contact use.

A screening-level (food only) analysis was conducted using established toxicological points of departure (PODs). Each end-use product results in different screening-level inputs and analysis results. There are no effects attributable to a single dose for DIMTS; therefore an acute population adjust dose was not established, and an acute dietary exposure assessment was not conducted. However, the chronic population adjusted dose (cPAD) is 0.002 mg/kg/day for DIMTS. Additional toxicity and residue chemistry data are anticipated to be required based on the result of the screening-level analyses.

Dietary Exposure Assessment – Paper Production

Three end-use product labels could result in indirect food contact to DIMTS: EPA Reg. Nos. 464-670, 464-672, and 464-673. The results have been presented here for the three products for both mold inhibition during paper production and for use in paper plant storage.

Paper Mold Inhibition During Production

For the use of DIMTS to prevent mold during paper production, the screening-level dietary risk assessment indicates that chronic dietary (food only) exposure and risk estimates exceed the level of concern (LOC) [i.e., >100% of the PAD] for some sub-populations for all the registered end-use products.

For the use of DIMTS to prevent mold during paper production, and assuming a food contact surface area of 2000 cm^2, the screening-level model for paper production results in a total estimated daily dietary intake of DIMTS less than 200 ppb for all three EPA Reg. Nos. 464-673, 464-672 and 464-670.

Mold Inhibition During Paper Plant Storage

DIMTS is approved for use in preserving finished paper or paper plant pulp, alum, broke, polymers, defoamers, emulsions, adhesives, paper mill coatings, pigments, and slurries. For these uses of DIMTS, the screening level dietary exposure analysis indicates that the chronic dietary (food only) exposure and risk estimates exceed the level of concern (LOC) [i.e., >100% of the PAD] for all population subgroups and all EPA registered end-use products.

For the use of DIMTS to prevent mold during paper plant preservation, and assuming a food contact surface area of 2000 cm^2, the screening-level model for paper production results in a total estimated daily dietary intake of DIMTS greater than 200 ppb for all population subgroups and registered labels; EPA Reg. Nos. 464-673, 464-672 and 464-670.

Dietary Exposure Assessment – Paper Production Using FDA Food Additive Regulation Level

The concentrations listed on EPA Reg. Nos. 464-673, 464-672 and 464-670 are greater than the currently established FDA food additive regulation under CFR 176.300, which only allows 0.2 lb DIMTS per ton of dry weight fiber. Using the assumption of 0.2 lb DIMTS per ton of dry weight fiber, the screening-level dietary exposure analysis for paper production indicates that the chronic dietary (food only) risk estimates do not exceed the level of concern (LOC) [i.e., < 100% of the PAD] for all population subgroups. Furthermore, using the FDA Food Additive Regulation Level for DIMTS and assuming a food contact surface area of 2000 cm^2, the screening-level model for paper production results in a total estimated daily dietary intake (EDI) of DIMTS less than 200 ppb for all population subgroups. If the registered DIMTS labels intend to treat paper that may contact food, the labels should be revised to comply with the FDA food additive regulation level of 0.2 lb a.i. per ton of dry weight fiber. If labels are not changed before the risk assessment for this registration review, the dietary assessment will be done using 395 ppm listed on the EPA labels.

Dietary Exposure Assessment – Adhesives

Two products containing DIMTS allow for use in adhesives and sealants; EPA Reg. Nos. 464-670 and 464-673. Use of DIMTS in sealants used in food packaging may result in DIMTS migrating into food indirectly. Therefore, a screening-level analysis was completed for DIMTS. The screening-level assessment was based on the FDA guidance and assumed that a maximum of seven ppb DIMTS may migrate from the food packaging adhesive into the food; which is a conservative estimate. Using these assumptions, the screening-level dietary exposure analysis for DIMTS in food-contact adhesives indicates that the chronic dietary (food only) risk estimates do not exceed the level of concern (LOC) [i.e., < 100% of the PAD] for all population subgroups.

Furthermore, the use of DIMTS in food contact adhesives and assuming a food contact surface area of 2000 cm^2, the screening-level model for adhesives results in a total estimated daily dietary intake (EDI) of DIMTS less than 200 ppb for all population subgroups and registered labels.

Dietary Exposure Assessment – Polymers

EPA Reg. No. 464-670 allows for use of DIMTS in plastic products that may contact food. Therefore, a screening-level analysis was completed for DIMTS in polymers. The assessment was conducted using the screening-level FDA model for food contact (hard surfaces) in commercial areas since no chemical-specific information on density was available. Additionally, the screening-level assessment assumed that 100% of the DIMTS residues in the plastics will migrate to food and a food contact surface of 4000 cm^2, which are conservative assumptions. The assessment was based on the registered product concentration of 0.8% DIMTS. Using these assumptions, the screening-level dietary exposure analysis for DIMTS in food-contact plastics indicates that the chronic dietary (food only) risk estimates exceed the level of concern (LOC) [i.e., > 100% of the PAD] for all population subgroups.

Furthermore, the use of DIMTS in food contact polymers and assuming a food contact surface area of 4000 cm^2, the screening-level model for plastics results in a total estimated daily dietary intake (EDI) of DIMTS greater than 200 ppb.

Conclusions & Data Requirements

The results of the screening-level analysis for paper mold inhibition, paper plant storage and preservation, and food-contact polymers using label-provided inputs result in risks above the agency's level of concern for some population subgroups. Additional residue data, including migration studies, residue analytical method for data collection (Guideline 860.1340), and storage stability studies (860.1380), are required because the level of concern is exceeded, per 40 CFR§158.2290. The labeled uses may need to be removed or revised during Registration Review if additional refinement data are not available for the risk assessment.

Additionally, the total daily dietary intake for chronic exposures for paper plant preservation and polymers is > 200 ppb for the US population and/or some population subgroups. Therefore, under 40CFR§158.2230, a total daily dietary intake greater than 200 ppb triggers toxicity data that should be submitted to the agency.

3.2.2 Drinking Water

DIMTS is also registered for use as a fungicide to control mold and sapstain fungi that cause discoloration and staining of freshly sawn lumber. It can also be applied to dimensional lumber, logs, plywood, Oriented Strand Board (OSB) and particle board to prevent surface mold growth. There are uncertainties with respect to DIMTS as well as its degradates entering drinking water based on the use patterns, the potential for exposure to surface water during manufacturing for the use as a materials preservative, and leaching of DIMTS from treated wood demonstrated in the available data.

The agency has not previously conducted a drinking water assessment for DIMTS and its degradates. Based on the registered uses, however, the agency cannot rule out the potential for exposure of humans to the parent DIMTS and/or its degradates in drinking water. Leaching of DIMTS from treated wood was demonstrated (MRID 47375907), and there is the potential for exposure to surface water during manufacturing for the use as a materials preservative. In addition, based on the water solubility values of parent DIMTS in Table 4 and the degradation products in Table 5 and observations in the anaerobic aquatic metabolism study (MRID 42177201), most environmental residues of DIMTS are expected to partition to water in the presence of soil and sediment. Moreover, the agency does not have adequate fate data on sorption of parent compound and its degradation products to determine the potential for contamination of drinking water. These fate data are anticipated to be required during registration review, as noted in Table 7 of this PWP. These data will be used to determine whether and to what extent DIMTS and its degradates pass through the WWTP that may result in human dietary exposure through drinking water which may trigger a drinking water assessment.

3.3 Occupational and Residential Exposures

The agency anticipates the need to update the occupational and residential exposure (ORE) assessment which was originally performed for the 2008 RED. The earlier ORE assessment from the RED will need to be revised to incorporate any revised toxicology endpoint selections and to utilize the exposure data anticipated to be received from the post-RED DCI.

3.3.1 Occupational Handler Exposure

EPA anticipates the need to revise the occupational handler assessment conducted in support of the 2008 RED. The ORE was conducted on March, 2008 (D344853). Occupational handler dermal and inhalation exposures to DIMTS were assessed in the RED for the following applications: liquid pour, liquid pump, solid pour, solid place, paintbrush/roller, pressure treatment, non-pressure treatment (dip and spray) and airless sprayer. The agency expects to conduct new assessments for liquid pour, solid pour, paintbrush/roller, pressure treatment and airless sprayer scenarios in registration review upon receipt of the anticipated exposure data expected from the RED DCI. These exposures were originally assessed using unit exposure data from the Pesticide Handler Exposure Database (PHED) and Chemical Manufacturer's Association (CMA) data in the RED.

Table 10 – Occupational Handler Exposure Scenarios for DIMTS

Scenario	Exposure Route(s)	Duration
Occupational Exposures		
Open Pour of Liquids for Material Preservatives*	Dermal Inhalation	Short and Intermediate Term
Solid Pour of Wettable Powders for Material Preservatives*	Dermal Inhalation	Short and Intermediate Term
Application of Paints and Stains (Brush/Roller and Airless Sprayer)	Dermal Inhalation	Short and Intermediate Term
Sapstain Dip for Wood Preservatives	Dermal Inhalation	Short, Intermediate and Long-term
Sapstain Spray for Wood Preservatives	Dermal Inhalation	Short, Intermediate, and Long-term
Pressure Treatment for Wood Preservatives	Dermal Inhalation	Short, Intermediate and Long-term

* material preservatives will include uses such as paints, adhesives and caulks, slurries, emulsions, plastics and vinyl products, leather tanning, and paper and paper board.

3.3.2 Occupational Post-application Exposure

Based on the low vapor pressure (~1E-6 mm Hg) of the active ingredient, EPA does not expect that DIMTS will volatilize in dry paint. Therefore, EPA will not conduct a post-application inhalation assessment for treated paint. Workers can be exposed to DIMTS while working at wood pressure plants and non-pressure treatment plants (sapstain dip and spray scenarios). The typical workers at pressure treatment facilities include tram setters, stacker operators, loader operators, QA/AC test borers, and tallymen. The typical workers at non-pressure treatment facilities includes chemical operators, loader operator, graders, millwrights, trim saw operators, and clean-up crews. Although worker exposure at pressure and non-pressure treatment plants

could be considered post-application, EPA will include these exposures collectively as occupational handler scenarios in registration review and will conduct an updated assessment in registration review for both the pressure treatment and non-pressure treatment scenarios upon receipt of the required data from the RED DCI.

3.3.3 Residential Handler Exposures

EPA anticipates the need to revise the residential handler assessment conducted in support of the 2008 RED. Residential handler dermal and inhalation exposures to DIMTS were assessed in the RED for paint brush/roller and airless spray application of paints and stains and finger painting (dermal). The quantitative exposure/risk assessment to be developed for residential handlers will be based on the following scenarios presented in Table 11.

Table 11 – Residential Handler Exposure Scenarios for DIMTS

Scenario	Exposure Route(s)	Duration
Residential Exposures		
Applications of paints and stains from brush/roller	Dermal Inhalation	Short Term
Applying of paints and stains from airless sprayer	Dermal Inhalation	Short Term

3.3.4 Residential Post-Application Exposures

EPA anticipates the need to revise the residential post-application assessment conducted in support of the 2008 RED. Residential post-application exposures result when adults and children come in contact with diiodomethyl p-tolyl sulfone in areas where pesticide end-use products have recently been applied (e.g., treated wood), or when children incidentally ingest the pesticide residues through mouthing the treated end-products/treated articles (i.e., hand-to-mouth of finger paints). The quantitative exposure/risk assessment to be developed for residential post-application exposure will be based on the following scenarios presented in Table 12. The agency required post-application data (indoor surface residue data, product use and description of product use) during the RED data call-in to support these uses. A residential post-application assessment for textiles and plastics will not be conducted because textile use is restricted to non-clothing use only and to carpet backing and plastics not to be manufactured into toys.

Table 12 – Residential Post-Application Exposure Scenarios for DIMTS

Scenario	Exposure Route(s)	Duration
Residential Exposures		
Post application exposure to toddlers from finger paints with preserved inks.	Dermal Incidental oral	Short Term
Post application exposure to toddlers from pressure treated wood used on decks and play sets	Dermal Incidental oral	Short Term

3.4 Aggregate and Cumulative Exposure

3.4.1 Aggregate Exposures

EPA anticipates the need to revise the aggregate assessment conducted in support of the 2005 RED. Upon a reevaluation and selection of toxicological endpoints, combined with the human health exposure assessments expected as a part of this registration review case, aggregate exposures will likely need to be assessed. This assessment is anticipated to include indirect chronic dietary (food and drinking water) (e.g., adhesives, paper/paper products and polymers) exposures and residential exposures (e.g., residential handler in paint and post-application exposures for wood treatment).

3.4.2 Cumulative Exposures

With respect to cumulative exposure, unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to DIMTS and any other substances, and DIMTS does not appear to produce a toxic metabolite produced by other substances. For the purposes of this registration review, therefore, EPA has not assumed that DIMTS has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see http://www.epa.gov/pesticides/cumulative/.

4 Environmental Risk Assessment

The agency anticipates the need to conduct an environmental risk assessment for DIMTS during registration review. Additionally, the agency anticipates the need to require additional ecological toxicity data for the registration review of DIMTS, based on the currently registered uses. There was an ecological hazard and environmental risk assessment conducted on November 1, 2007 in support of the RED.[1]

The agency has not previously conducted a risk assessment that supports a complete endangered species determination for DIMTS. The ecological risk assessment planned during registration review will allow the agency to determine potential acute and chronic risks to aquatic organisms exposed to DIMTS and its degradates that are transported from treatment sites into the aquatic environment. Such sites include antisapstain uses, leather tanning, paint preservation, adhesives, caulks, and sealants, rubber and plastics, paper production, and paper preservation during storage. All uses are assumed to have the potential to result in Down-the-Drain (DtD) exposure. In addition, the wood preservation and paper production use and the paint preservation use have the potential to result in runoff into the aquatic environment. Sorption and bioconcentration of all residues are expected to be limited. The risk assessment will also allow the agency to determine whether each use of the DIMTS has 'no effect' or 'may affect' federally listed threatened or endangered species (listed species) or their designated critical habitats. When an assessment concludes that a pesticide's use 'may affect' a listed species or its designated critical

[1] Mostaghimi and Erickson.

habitat, the agency will consult with the U.S. Fish and Wildlife Service and/or National Marine Fisheries Services (the Services), as appropriate.

4.1 Environmental Fate Assessment

The environmental fate assessment will address the persistence and mobility of parent DIMTS and the degradates MIMPTS, MPTS, and PTSOA.

DIMTS is stable to hydrolysis at pH 5, but degrades with half-lives of 2.1 days at pH 7 and 3.4 days at pH 9 (MRID 43008701). It degraded rapidly in irradiated water with a half-life of 1.4 hour (MRID 47343001)); however, photodegradation is expected to be limited because of the lack of light penetration caused by suspended sediment and shading. Photodegradation on soil occurred with a half-life of 5.3 days (MRID 47323601). In soil, DIMTS is rapidly degraded with half-lives of 1.5 day under aerobic conditions (MRID 41765405) and 4.2 days under anaerobic conditions (MRID 41765406). Under anaerobic aquatic conditions representing bottom sediment, DIMTS degraded with a half-life of 9.6 days and residues are expected to partition to water rather than sediment (MRID 42177201). Data on parent DIMTS have not been submitted for leaching-adsorption-desorption and are anticipated to be required.

In the environment, DIMTS is relatively insoluble (<2 mg/l, Table 4), but will largely partition to water in the presence of sediment based on the results of the environmental fate data in Appendix B. Even with its relatively low water solubility, DIMTS is not likely to bioconcentrate in aquatic organisms based on its log P value of 2.66 (<3, Table 4). Based on its low vapor pressure and Henry's law constant (Table 4), it is unlikely to move from soil or water into air. Although the water solubility of parent DIMTS is lower than for the degradates (Table 5), the environmental behavior of the degradates is expected to be similar to parent compound.

The degradates of DIMTS do not completely mineralize in the environment. MIMPTS was a terminal degradate (~10 % of applied parent) for photodegradation in water, but degraded with half-lives of 12.5 days in irradiated soil, 32 days in aerobic soil, 21 days in anaerobic soil, and 11 days in the anaerobic aquatic metabolism studies. MPTS was a minor degradate in the hydrolysis study, did not degrade in the photodegradation in water or the anaerobic soil and anaerobic aquatic metabolism studies, and was relatively persistent in aerobic soil with a half-life of 53 days. PTSOA was the main terminal degradate (~90 % of applied parent) in the photodegradation in water study and was a minor degradate in the hydrolysis study. Acceptable data on leaching-adsorption-desorption in soils and sediment have not been submitted for MIMPTS and MPTS and are anticipated to be required. Leaching-adsorption-desorption data on PTSOA are not anticipated to be required because the only study with significant quantities of PTSOA formed was photodegradation in water, and this route of dissipation is expected to be limited because of suspended sediment and shading.

Based on a wood leaching study using submerged blocks (MRID 47375907), DIMTS leached from treated wood (5.6 mg/cm^3) with maximum, minimum, and average rates of 23.5, 19.1, and 20.4 µg/cm^2/day and cumulative rates of 309 µg/cm^2. The leached portion of DIMTS was 17.9 % (Table B1). The leaching rate was relatively constant in the study. These leaching rates are the most relevant because the treatment rate in the study (1 % w/w) was the closest to 0.12-0.32 % w/w rate in Label Reg. No. 464-673.

4.1.1 Waste Water Treatment Plants (WWTP)

DIMTS was readily biodegradable in WWTP simulations studies at 0.05 and 0.5 mg/L (MRID 47024601) but was not readily biodegradable at 28-67 mg/L (MRID 47338401). Even though DIMTS was readily biodegradable in MRID 47024601, DIMTS was only primarily biodegradable but not ultimately biodegradable at 0.05 and 0.5 mg/L because the test material primarily formed terminal degradates other than CO_2 and water. The half-lives of the degradate MIMPTS were 1.2 day at 0.05 mg/L and 12.6 days at 0.5 mg/L. The degradate MPTS did not degrade in MRID 47024601. In a modified Zahn-Wellens test (OECD 302B), the degradate MPTS was studied as a parent compound, and was not ultimately biodegradable because only about 48 % (<70 %) of dissolved organic carbon (DOC) was removed in 28 days (MRID 47375909). In an ASRI study (MRID 47373803), DIMTS was not toxic to WWTP organisms when tested at up to >4.5 times the water solubility (<2 mg/L, Table 4). Because DIMTS is not expected to reach concentrations as high as 9 mg/L based on its solubility of <2 mg/L, no further ASRI testing is needed for DIMTS or its degradates.

4.1.2 Water Quality

DIMTS and its degradates are not identified as a cause of impairment for any water bodies listed as impaired under section 303(d) of the Clean Water Act. [2] In addition, no Total Maximum Daily Loads (TMDL) have been developed for DIMTS and its degradates. [3] More information on impaired water bodies and TMDLs can be found at EPA's website. [4]

4.2 Conceptual Models for Environmental Exposure Pathways

Based on the registered use of DIMTS as well as physical/chemical properties and environmental fate data for DIMTS and its degradates, the agency cannot rule out the possibility that aquatic organisms downstream of wastewater treatment facilities that receive discharges have the potential to be exposed to DIMTS and/or its degradates. The agency has created conceptual models for potential routes of environmental exposure which are included in "Conceptual Models for Environmental Exposure Pathways of Antimicrobial Pesticides", found in the docket at www.regulations.gov, EPA-HQ-OPP-2014-0638-0002. A conceptual model of pulp and paper mill systems can be found on page 26, and for the antisapstain use, may be seen on p. 29. Conceptual models for textiles (including rubber, plastics, and leather) may be seen on pp. 15-16, and for adhesives, caulks, and sealants, may be seen on p. 17. Based on the summary of registered uses of DIMTS presented in Table 6, the chemical/physical properties of parent DIMTS in Table 4 and the degradates in Table 5, and the environmental fate data presented in Appendix B, the agency has developed conceptual model diagrams for exposure of ecological organisms to DIMTS and its major degradates.

In the environmental fate studies, DIMTS forms MIMPTS and MPTS degradates, which are more persistent and water soluble than the parent compound. The PTSOA degradate, while also

[2] http://iaspub.epa.gov/tmdl_waters10/attains_nation_cy.cause_detail_303d?p_cause_group_id=885
[3] http://iaspub.epa.gov/tmdl_waters10/attains_nation.tmdl_pollutant_detail?p_pollutant_group_id=885&p_pollutant_group_name=PESTICIDES
[4] http://www.epa.gov/owow/tmdl/

formed, was only detected at significant concentrations in the photodegradation in water study, and this route of dissipation is expected to be limited because of suspended sediment and shading in surface water. Therefore, PTSOA is not expected to be included in the planned risk assessment. MPTS is the terminal degradate under most environmental conditions and did not mineralize in a Zahn-Wellens biodegradation simulation test (MRID 47375909). As a result, MPTS is expected to be present in the water phase of effluent with Down-the-Drain exposure and from treated paint used outdoors.

The screening-level risk assessment that will be conducted as part of this registration review will evaluate potential risks to ecological organisms from exposure to parent DIMTS and the degradates MIMPTS and MPTS.

4.3 Ecological Effects Assessment

4.3.1 Mechanism of Action

In diiodomethyl p-tolyl sulfone, the bonds between the methyl carbon and both halogen substituents are highly polarized by the electronegative iodide and sulfone groups, destabilizing the bonds and contributing to their partial ionic character. The toxicity of the chemical results from the successive liberation of each halide substituent. Free iodide may then react with nucleic acids, fatty acids, and proteins.

In vertebrates, iodine complexes with the amino acid tyrosine to form hormones with important roles in the regulation of homeostasis, growth and development, and metabolism. Some effects in vertebrates may result from the influence of excess iodine on the production of these hormones.

4.3.2 Measures of Effect (Ecotoxicology Endpoints)

Ecotoxicity endpoint data are used as measures of effects to aquatic and terrestrial organisms. All available ecotoxicity endpoints in the agency's files for DIMTS studies submitted by registrants or other interested parties, federal laboratory data, or from the public literature are tabulated in Appendix C along with the data requirements and data gaps. There are currently no ecotoxicity data for DIMTS degradates. The most sensitive values for each receptor group used for the previous risk assessment are seen in Table 13. These selected endpoints will be updated during the risk assessment phase for registration review based on any additional submitted data or data found in the public literature.

Table 13 – Selected Ecological Effects Endpoints for Risk Assessment of DIMTS

Receptor Group	Surrogate Species	Risk Scenario	Toxicity Endpoint	Reference (MRID)
Freshwater fish	Rainbow trout	Acute	96-h LC_{50} = 66.7 ug/L	47234001
	Rainbow trout	Chronic	Data Gap	--
Freshwater invertebrates	Daphnia magna	Acute	48-h EC_{50} = 279 ug/L	47234002
		Chronic	Data Gap	--
Estuarine/marine fish	Sheepshead minnow	Acute	Data Gap	--
		Chronic	Not required[A]	--

Receptor Group	Surrogate Species	Risk Scenario	Toxicity Endpoint	Reference (MRID)
Estuarine/marine invertebrates	Eastern oyster	Acute	Data Gap	--
	Mysid Shrimp	Acute	Data Gap	--
		Chronic	Not required[A]	--
Algae	Green alga	Non-listed	Data Gap	--
Blue-Green Algae	Cyanobacteria	Non-listed	Data Gap	--
Aquatic vascular plants	Duckweed	Non-listed	Data Gap	--
Seedling Emergence	Rice	Non-listed	Not required[B]	--
Vegetative vigor	Rice	Non-listed	Not required[B]	--
Birds	Northern bobwhite quail	Acute	LD_{50} = >2000 mg/kg	123643
	Mallard duck	Subacute dietary	LC_{50} = >5620 mg/kg	124488
		Chronic	Not required[A]	--
Mammals	See Table 9[C]	Acute	LD_{50} = >5000 mg/kg (males) LD_{50} = >5000 mg/kg (females)	41765401,43608702, 42586801
		Chronic	NOAEL = 10 mg/kg/day	46913301
Nontarget insects	Honey bee	Acute	Data Gap	--

[A] Not required for this use pattern.
[B] Not required. No significant exposure anticipated.
[C]Test species used in Human Health Risk Assessment will be used as surrogates for mammalian ecotoxicity assessment.

4.4 Exposure Analysis Plan

4.4.1 Aquatic and Terrestrial Wildlife Exposure Estimates

Available models will be used to determine the estimated environmental concentration (EECs) in the aquatic environment. Resulting exposure estimates will be compared to the toxicity endpoints to determine if levels of concern are exceeded for each receptor group.

4.4.2 Screening Level Down-the-Drain Analysis

The Down-the-Drain (DtD) module of E-FAST (Exposure and Fate Assessment Screening Tool) was used to determine the potential for aquatic organisms downstream of domestic wastewater treatment plants that receive discharges from end-use of DIMTS to be exposed to DIMTS and its degradates. The results of the DtD module runs are expressed as number of days of exceedance of concentrations of concern (COC) for aquatic organisms. A detailed description of derivation of data for input parameters selected to run the DtD module and of the theoretical basis for this model is presented in Appendix E. A conservative assumption of no removal during wastewater treatment was used in DtD model runs.

The DtD analysis for DIMTS is intended to serve two purposes: (1) to demonstrate the maximum WWTP influent volume of DIMTS that would trigger potential concerns for aquatic organisms exposed to DIMTS or its degradates downstream of domestic wastewater treatment plants and (2) to evaluate potential exposures based on the assumptions that the total production volume of DIMTS enters domestic wastewater treatment plants. A key purpose of the DtD analysis for DIMTS is to determine the lowest maximum annual WWTP influent volumes of DIMTS that would trigger potential concerns for aquatic organisms downstream of domestic WWTPs.

Table 14 presents results of a screening-level DtD analysis for DIMTS which is based on laboratory toxicity data for freshwater organisms. Based on these aquatic toxicity data and the estimated production volume which is expected to be no greater than 250,000 kilograms per year, the DtD model predicted 89 days per year exceedances of concentrations of concern for endangered freshwater fish (acute). However, using the average case scenarios, the exceedance for endangered fresh water fish (acute) was less than 10 days per year.

Table 14 – Summary of Screening Level Down-the-Drain Analysis Results for Aquatic Organisms

High End Scenario		
WWTP Influent Volume	**Freshwater Fish Acute (COC = 33.35 ug/L)**	**Endangered Freshwater Fish Acute (COC = 3.33 ug/L)**
250,000 kilograms/year	Exceeded 2 days per year	Exceeded 89 days per year
WWTP Influent Volume	**Freshwater Invertebrates Acute (COC = 139.5 ug/L)**	**Endangered Freshwater Invertebrates Acute (COC = 13.95 ug/L)**
250,000 kilograms/year	No exceedance	Exceeded 13 days per year
Average –Case Scenario		
WWTP Influent Volume	**Freshwater Fish Acute (COC = 33.35 ug/L)**	**Endangered Freshwater Fish Acute (COC = 3.33 ug/L)**
250,000 kilograms/year	Exceeded less than a day per year	Exceeded 10 days per year
WWTP Influent Volume	**Freshwater Invertebrates Acute (COC = 139.5 ug/L)**	**Endangered Freshwater Invertebrates Acute (COC = 13.95 ug/L)**
250,000 kilograms/year	No exceedance	Exceeded 1 day per year

This screening level analysis assumes that DIMTS and degradates are released to domestic wastewater treatment plants. Based on registered uses of DIMTS and degradates presented in Table 6 of this PWP, there are some uses, such as paper production, for which discharges may enter industrial WWTPs rather than domestic WWTPs prior to entering surface water. Different

methods and tools for assessing potential exposures and associated ecological risks will be applied for these other types of uses.

4.5 Effects Analysis Plan

Additional open literature studies will be identified through EPA's ECOTOXicology (ECOTOX) database. The ECOTOX database will be searched during the risk assessment phase of DIMTS and the data reviewed following the agency's policy for reviewing public literature for use in assessing risks from pesticides. Those ecotoxicity values found in the public literature to be more sensitive than those currently in Table 13 and or which satisfy an existing data gap(s) will be used during the risk assessment phase of DIMTS to update Table 13. ECOTOX was created and is maintained by the USEPA, Office of Research and Development, and the National Health and Environmental Effects Research Laboratory's (NHERL) Mid-Continent Ecology Division.

5 Endocrine Disruptor Screening Program (EDSP)

As required by FIFRA and FFDCA, EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of its reregistration decision for DIMTS, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), DIMTS is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. A second list of chemicals

identified for EDSP screening was published on June 14, 2013[5] and includes some pesticides scheduled for registration review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors.

For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website.[6]

6 Optional Label Changes

The agency invites comment on any label amendments that could be considered to eliminate the anticipated need for EPA to require certain data, reduce the possibility that EPA's planned risk assessments overestimate risk due to reliance on conservative assumptions, and/or improve label clarity. Additionally, as discussed in Section 3.2.1., if the registered DIMTS labels intend to treat paper that may contact food, the labels should be revised to comply with the FDA food additive regulation level of 0.2 lb a.i. per ton of dry weight fiber.

7 Guidance for Commenters

7.1 Preliminary Work Plan

The public is invited to comment on EPA's Preliminary Work Plan and rationale. The agency will carefully consider all comments as well as any additional information or data provided in a timely manner prior to issuing a final work plan for the DIMTS registration review case.

7.1.1 Trade Irritants

Through the registration review process, the agency intends to solicit information on trade irritants and, to the extent feasible, take steps toward facilitating irritant resolution. The agency will work to harmonize tolerances and international maximum residue limits (MRLs) and may modify tolerance levels to do so, when possible. **Stakeholders are asked to comment** on any trade irritant issues resulting from lack of MRLs or disparities between U.S. tolerances and MRLs in key export markets, providing as much specificity as possible regarding the nature of the concern.

7.1.2 Water Quality

The agency invites submission of water quality data for this pesticide. To the extent possible, data should conform to the quality standards in Appendix A of the *OPP Standard Operating Procedure: Inclusion of Impaired Water Body and Other Water Quality Data in OPP's Registration Review Risk Assessment and Management Process*[7] in order to ensure they can be used quantitatively or qualitatively in pesticide risk assessments.

[5] See http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2009-0477-0074 for the final second list of chemicals.
[6] http://www.epa.gov/endo/.
[7] http://www.epa.gov/oppsrrd1/registration_review/water_quality_sop.htm.

7.1.3 Environmental Justice

EPA seeks to achieve environmental justice, the fair treatment and meaningful involvement of all people, regardless of race, color, national origin, or income, in the development, implementation, and enforcement of environmental laws, regulations, and policies. To help address potential environmental justice issues, the agency seeks information on any groups or segments of the population who, as a result of their location, cultural practices, or other factors, may have atypical, unusually high exposure to DIMTS compared to the general population. **Please comment if you are aware of any sub-populations that may have atypical, unusually high exposure compared to the general population.**

7.1.4 Structure Activity Relationships

EPA must rely upon information of appropriate quality and reliability for each decision made by the agency. In the OPP, the evaluation process for a pesticide chemical traditionally begins with the applicant's submission of a set of studies conducted with the specific pesticide chemical of interest. The use of the results of such testing (measured data) is a logical, scientifically rigorous process that identifies the physical, chemical, and environmental fate properties of the pesticide, as well as the dose and endpoints at which an adverse effect can occur in various animal species.

Today, there is significant interest in alternative techniques, i.e., techniques other than data generation that could significantly inform the agency's decision-making process. Recently, OPP has made increasing use of structure activity relationship (SAR) as part of its regulatory decision-making process. In the SAR process, a chemical's molecular structure is compared to that of other chemicals for which data are available. These structural similarities are then used to make predictive judgments about a chemical's physical, chemical, and biological properties. Thus, the chemical's physical, chemical, and biological properties are a function of (or directly related to) the chemical's molecular structure. Quantitative SAR is referred to as QSAR. To develop a QSAR, a selected set of measured data on a single physical, chemical, or biological property is used to derive a model (an equation) to predict the value of that property.

Since SAR assessments and QSAR modeling are another set of tools that are available to agency scientists, OPP has begun a process shift that envisions shifting from the current study-by-study approach to an approach in which the use of predicted data, generated using validated models, is considered along with information from open literature and studies specifically generated under Part 161 requirements. All relevant information would be considered as part of a weight-of-the-evidence evaluation.

At this time, EPA believes that for certain endpoints, especially physical/chemical and fate properties, that SAR and QSAR might be effectively utilized to fulfill these data requirements for many antimicrobial pesticide chemicals. When considering biological properties, at this time, EPA believes that SAR and QSAR can be most effectively utilized in the evaluation of chemicals that exhibit lower toxicity for human health and/or ecotoxicity parameters. This is appropriate because the risk assessment for lower toxicity chemicals can be stream-lined, i.e., a screening-level assessment procedure rather than multiple tiers of assessments with progressively more data requirements.

If stakeholders believe that submission of predicted data can fulfill one of the data needs for the DIMTS case, then the agency invites submission of this information. The submitter would be expected to supply a rationale describing the utility of the information and provide documentation on the scientific validity of the information. The determination that the predicted data fulfills the data requirement would be at the sole discretion of the agency. Pre-submission consultation with the agency is encouraged.

7.1.5 Additional Information

Stakeholders are also specifically asked to provide available information and data that will assist the agency in refining its risk assessments, including any species-specific ecological effects determinations. The agency is interested in receiving the following information:

1. Confirmation on the following label information:
    A. Sites of application
    B. Formulations
    C. Application methods and equipment
    D. Maximum application rates
    E. Frequency of application, application intervals and maximum number of applications
    F. Geographic limitations on use
2. Use or potential use distribution
3. Use history
4. Usage/use information for non-agricultural uses (e.g., materials preservation)
5. Typical application interval
6. State or local use restrictions
7. Ecological incidents (non-target plant damage and avian, fish, reptilian, amphibian and mammalian mortalities) not already reported to the agency
8. Monitoring data

8 Next Steps

After the 60-day comment period closes in November 2015, the agency will review and respond to any comments received and then issue a Final Work Plan for the DIMTS case.

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Appendix A Toxicology Profile

Acute Toxicity for Product Labeling

As listed in Table A1, diiodomethyl p-tolyl sulfone was found to be minimally toxic for acute oral and dermal toxicity (Toxicity Category IV for both) and low toxic for inhalation toxicity (Toxicity Category III). It caused severe irritation to the ocular tissue of rabbits (Category I) but minimal irritation to the skin of rabbits (Category IV). Diiodomethyl p-tolyl sulfone is a dermal sensitizer.

Table A1 – Acute Toxicity Studies for Diiodomethyl p-tolyl Sulfone

Guideline No./ Study Type	MRID No.	Results	Toxicity Category
870.1100/ Acute oral toxicity	41765401/43008702	LD50 >5000 mg/kg for both males and females	IV
870.1200/ Acute dermal toxicity	00123023	LD50 (male rats) > 20000 mg/kg	IV
870.1300/ Acute inhalation toxicity	43660901 & 00087842	LC_{50} (combined)= 0.96 mg/L LC_{50} (male) = 1.15 mg/L LC_{50} (female) = 0.77 mg/L	III
870.2400/ Acute eye irritation	41765402/43008703	Severe irritant (rabbit)	I
870.2500/ Acute dermal irritation	41765403/43008704	Minimum irritant (rabbit)	IV
870.2600/ Skin sensitization	48293901	A dermal sensitizer	

Subchronic Toxicity

Adequacy of Database for Subchronic Toxicity: The database for subchronic toxicity is considered adequate. There are several studies in the agency's hazard database to address subchronic oral toxicity, including two 90-day oral (diet) toxicity studies in rats (MRIDs 42054402/43246401 and 47338201), a 90-day oral (capsule) toxicity study in dogs (MRID 42054403/43246402), a 28-day dermal study in rats (MRID 48236901), and a 90-day inhalation toxicity study (MRID 48264901). A brief summary of each of the studies is provided below.

870.3100 90-Day (13-Week) Oral Toxicity – Rat

(1) In a subchronic oral toxicity study (MRID 42054402/43246401), groups of Crl:CD(SD)BR rats (10/sex/group) received the test material diiodomethyl p-tolyl sulfone (≥ 95% a.i.; Lot #68-332-CB) at concentrations of 0, 5, 20, or 80 (15/sex) mg/kg/day, in the diet, for 90-94 days.

No significant difference in body weight and mean weight gains were noted among treatment groups. The only significant findings in the treated animals were statistically significant

elevations in mean phosphorus and cholesterol levels in the high dose group males and squamous metaplasia of the salivary gland ducts in three males in the high dose group. All of the effects noticed in the treatment groups were not considered toxicologically significant. The highest dose does not reach the maximum tolerated dose (MTD). The study is classified as **Core-Minimum** and can be considered for hazard assessment.

(2) In a subchronic oral toxicity study (MRID 47338201), groups of Sprague-Dawley (CD) rats (8/sex/group) received the test material diiodomethyl p-tolyl sulfone (97.4±0.01% a.i.; Lot # PB1631LA01) at concentrations of 0, 5, 20, 100, or 250 mg/kg/day, in the diet, for at least 13 weeks. Data generated in this study were used to establish the doses for a subsequent two-generation reproduction study.

There were no treatment-related deaths or signs of clinic toxicity. Feed consumption was significantly decreased during the first half of the study in males in the two high-dose groups and in females in the highest dose group, accompanied with a lower termination body weight (approximately 10% relative to the controls) in both the highest dose males and females.

Slightly higher liver and salivary glands weights were noted in rats in the highest dose group compared to the controls, with the relative weights of these organs statistically identified. Histopathological alterations were noted in the stomach, liver, and salivary glands of the highest dose animals, including hyperplasia of the non-glandular mucosa in all highest dose (250 mg/kg/day) animals with erosions, ulcers or inflammatory changes, generalized slight hypertrophy of the hepatocytes, and squamous metaplasia of the salivary gland ducts, primarily the intra-lobular duct of the submandibular gland. Some rats given 100 mg/kg/day also exhibited hyperplasia of the non-glandular mucosa of the stomach and squamous metaplasia of the salivary glands. “Based on these data, the no-observed-adverse effect level (NOAEL) was considered to be 20 mg/kg/day.” A final conclusion will be provided after the agency’s comprehensive review of the study.

870.3150 90-Day (13-Week) Oral Toxicity – Dog

In a subchronic oral toxicity study (MRID 42054403/43246402), groups of beagle dogs (4/sex/group) were administered the test material diiodomethyl p-tolyl sulfone (($\geq$ 95% a.i.; Lot # 68-332-CB) at doses of 0, 2, 10, or 60 mg/kg/day, in gelatin capsules, for 96-100 days.

Clinical signs of toxicity, which were observed 1-4 hours after dosing in the high dosage group, included decreases activity, dehydration, mucoid eye discharge, weakened condition and abnormal feces (mucoid and occasionally blood-tinged). Eye discharge and abnormal feces in the intermediate dosage group were also considered treatment related.

Females in the high dosage group had at least 20% decreases in mean body weight gain, in comparison to the control value, from day 0 to 91.

Mean hematology evaluations of the treated animals were not statistically significant from those of the control animals, although the white blood cell count and neutrophil counts of the males in the 60 mg/kg/day group were higher than the control and other treated groups. The high dosage group males also had significantly decreased mean calcium, albumin, albumin:globulin ratio, and total protein values on one of two evaluations during the treatment period.

On gross necropsy, the only findings were changes in the gastrointestinal tract (patchy-red discoloration of the stomach and mucoid appearance of the small intestines) in three males in the high dosage group. Absolute and relative organ weight did not differ from the control values.

On histopathology, degeneration of the thyroid gland (mineralization within colloid clumping of sloughed follicular cells and colloid depletion) was observed in males and females in the high and intermediate dosage groups. Sialadenitis (ductal and periductal inflammation of the salivary gland), hemorrhagic gastritis, necrosis of the small intestine and keratitis were also observed in the high dose group.

The no-observed-adverse-effect-level (**NOAEL**) was determined to be **2 mg/kg/day**, based on histopathological changes observed in the thyroid glands, salivary gland and gastrointestinal (GI) tract.

The study is classified as **Core-Minimum** and can be considered for hazard assessment.

870.3200 Subchronic (21/28-day dermal) Toxicity

(1) In a subchronic dermal study (MRID 48236901), diiodomethyl p-tolyl sulfone (purity 97.7%, Lot # PB1631LA01) was applied to a semi-occluded skin of 10 Crl:CD(SD) rats/sex/dose at dose levels of 0, 20, 100, or 500 mg/kg bw/day, 6 hours/day, 7 days/week, for 28 consecutive days. The animals were acclimated to dermal wraps for three days prior to dosing. The fur of each test animal was clipped from the dorsal area of the trunk over an area of at least 10% of the body surface, starting at the scapulae (shoulders) to the wing of the ilium (hipbone) and half way down to the flank on each side of each animal.

There were no compound-related effects in body weights, body weight gains or feed consumption in dosed male and female animals as compared to the controls.

Systemic effects related to the treatment included increased absolute and relative thyroid weights in high-dose males. Thyroid histopathologic changes were observed in all treated males and females in the mid- and high-dose groups. The thyroid effects included very slight hypertrophy of thyroid follicular epithelial cells and altered tinctorial properties of the colloid, characterized by the presence of pale to very pale eosinophilic colloid in the follicles of treated male and female animals as compared to the bright eosinophilic and homogeneous colloid in the controls.

Dermal reactions attributed to the test compound were observed in the high-dose males including scratches, very slight edema, scabs of varying severities, and slight scaling. Similar dermal observations, as well as erythema, were reported in females in the mid- and high-dose groups. Necropsy and histopathological findings in the high-dose males and the mid- and high-dose females, at the dermal application site, were multifocal scabs, slight epidermal hyperplasia (acanthosis) with very slight parakeratosis, and very slight multifocal subacute to chronic inflammation in the dermis. The histopathology of the treatment-related scabs at the dermal application site consisted of multifocal epidermal ulceration, moderate epidermal hyperplasia, slight hyperkeratosis with parakeratosis, subcorneal pustules in the epidermis, and slight subacute to chronic multifocal inflammation of the dermis, which were attributed to scratching of the treated skin due to irritation of the test compound.

Additional changes considered to be secondary to the treatment-related ulcerative dermal lesions were marginally higher serum aspartate aminotransferase activity in mid- and high-dose females, and very slight myeloid cell hyperplasia in the bone marrow, very slight splenic extramedullary hematopoiesis, and increased white blood cell count with increased percentage of neutrophil cells in high-dose females.

The **NOAEL for systemic toxicity** is **20 mg/kg/day** for females, based on thyroid effects but is **not established for males.** The **NOAEL for dermal effects** is **20 mg/kg/day for both males and females.**

This 28-day dermal toxicity study in the rat is classified **Acceptable/Guideline** and satisfies the guideline requirement for a 28-day dermal toxicity study (OPPTS 870.3200; OECD 410) in rats.

870.3465 Subchronic (90-day inhalation) Toxicity – Rat

In a subchronic inhalation study (MRID 48264901), 1-((Diiodomethyl)sulfonyl)-4-methyl-benzene (97.3% a.i.; Lot # PB1631LA01) was administered to 10 Crl:CD(SD)rats/sex/concentration by dynamic nose-only exposure at analytic concentrations of 0, 1, 7, or 30 mg/m^3 for 6 hours/day, 5 days/week, for 13 weeks (65 total exposure days). The average mass median aerodynamic diameter (MMAD) of the test material aerosol was 2.6, 2.7, and 2.6 µm for exposure concentration groups 1, 7, and 30 mg/m^3, respectively.

Nine deaths occurred during the exposure phase of the study. These deaths included: two control males, one control female, one mid-concentration male, five high-concentration males, and one high-concentration female. Study authors did not report whether deaths in the high concentration groups were considered treatment related. Gross pathology observations were performed in only the high-concentration group males and revealed mottled lungs and failure of lung deflation. No treatment-related changes regarding food consumption, in-life body weights, ophthalmology, clinical chemistry, or coagulation parameters were observed. The mid- and high-concentration group males and females were observed with a slight, unilateral or bilateral parakeratosis with inflammation of the ventral meatus of the anterior nasal cavity. All affected males and females were also observed with irritation of the nasal septum. There were other treatment-related effects in the nasolacrimal duct, larynx, and trachea in males and females of the highest concentration group, including degeneration with or without inflammation, necrosis, and necrotizing inflammation.

In addition, 4 of 10 high-concentration males were observed with moderate to severe necrotizing bronchioalveolar inflammation of the lungs. Most high-concentration group males and females exhibited inflammation of the alveolar septa. Minor treatment-related systemic effects were observed in the thyroid glands (colloid with altered tinctorial properties) of males and females exposed to mid to high concentrations of the test material.

High-concentration group males had hemoglobin and hematocrit levels that were statistically significantly higher than controls. Although considered treatment related, these levels were not interpreted to be toxicologically relevant by study authors. High-concentration group female rats had a slight increase in neutrophils, and this increase was considered treatment related. In addition, these female rats had an increase in alanine aminotransferase (ALT) and a non-

statistically identified increase in aspartate aminotransferase (AST) without accompanying histopathological changes in the liver.

Terminal body weights for high-concentration group males were decreased relative to controls, but although this difference was not statistically significant, study authors considered it related to treatment. The high-concentration group males were the only group to have a statistically significant organ weight alteration, which was an increase in mean lung weight.

The LOAEC is 7 mg/m^3, based on minor systemic effects in the thyroid glands and parakeratosis with inflammation in the anterior nasal cavity in both male and female rats. The NOAEC is 1 mg/m^3.

This subchronic inhalation toxicity study in the rat is classified **Acceptable/Guideline** and satisfies the guideline requirement for a subchronic inhalation study OPPTS 870.3465; OECD 413 in the rat.

Developmental Toxicity

Adequacy of Database for Developmental Toxicity: There are several studies in the agency's hazard database to address developmental toxicity in both species, rats (MRIDs 42054404/42054405/43246403 and 47373805) and rabbits (MRIDs 42243801/43246404, 47242202, and 47214601). The available studies appear adequate, and a brief summary of each of the studies is provided below.

870.3700a Prenatal Developmental Toxicity (Gavage) Study – Rat

(1) In a developmental toxicity study (MRIDs 42054404/42054405/43246403), Crl:CD®(SD)BR albino rats (22/group) received 0, 100, 300, or 1000 mg/kg/day diiodomethyl p-tolyl sulfone (95% a.i; Lot No. 66-207-CB) by oral gavage from gestation days 6 through 15. Another developmental toxicity study (MRID 42054405) was conducted using the same strain of Crl:CD®(SD)BR albino rats (25/group) receiving the same test substance diiodomethyl p-tolyl sulfone (95% a.i; Lot No. 66-207-CB) at 0 or 1000 mg/kg/day by oral gavage from gestation days 6 through 15.

Maternal toxicity was evident as reduced body weight gain and food consumption in the mid and high dose groups and as increased clinical signs of toxicity in the high dose group. **The maternal toxicity LOAEL is 300 mg/kg/day and the maternal toxicity NOAEL is 100 mg/kg/day, based on reduced body weight gain and food consumption.**

Developmental toxicity was noted in the high dose group as slightly decreased mean litter size, increased number of resorptions relative to the number of implantation sites, reduced mean fetal body weight, increased incidences of umbilical hernia and incomplete ossification of the supraoccipital bones. **The developmental toxicity LOAEL is 1000 mg/kg/day and the developmental toxicity NOAEL is 300 mg/kg/day, based on decreased mean litter size, increased number of resorptions relative to the number of implantation sites, reduced mean**

fetal body weight, increased incidences of umbilical hernia, and incomplete ossification of the supraoccipital bones.

The study is classified **Core-Guideline** and satisfies the guideline requirement (OCSPP 870.3700), developmental toxicity (teratology) study in rats.

(2) In a developmental toxicity study in rats published by Ema et al (MRID 47373805 [Ema et al, 1992]), pregnant Wistar rats (22/group) were administered diiodomethyl p-tolyl sulfone (>95% a.i.) at doses of 0, 0.125, 0.25, 0.5 or 1.0% in the diet on gestational days 6-15. The estimated daily intakes of diiodomethyl p-tolyl sulfone were 0, 100, 182, 288, or 411 mg/kg/day, respectively. Significant lower maternal body weight gain and food consumption were observed in the 0.25, 0.5 and 1.0% groups during the administration period. No significant changes induced by the test substance were detected in the numbers of resorption, fetal death, or body weight of live fetuses. No evidence of teratogenesis was revealed in fetuses during morphological examination.

870.3700b Prenatal Developmental Toxicity (Gavage) Study – Rabbit

(1) In a developmental toxicity study (MRIDs 42243801/43246404), pregnant New Zealand White rabbits received 0, 4, 15, or 60 mg/kg bw/day diiodomethyl-p-tolylsulfone (95% a.i.; Lot No. 66-207-CB) by oral gavage from gestation day 6 through 18, inclusive.

Maternal toxicity was noted as deaths and abortions primarily in the high dose group, clinical signs in the mid and high dose group, reduced body weight gain and food consumption in the mid and high dose groups. **The maternal toxicity LOAEL is 15 mg/kg/day and the maternal toxicity NOAEL is 4 mg/kg/day, based on clinical signs (deaths) and decreased body weight gain and food consumption.**

Developmental toxicity was noted in the mid and high dose in the form of decreased mean litter size, increased number of resorptions relative to the number of implantation sites as degenerating fetuses, and decreased postnatal survival and reduced mean fetal body weight in the mid dose (data only available for mid dose). At the mid dose, developmental effects also occurred in the form of increased incidences of hydrocephalus (which was also noted at a low incidence in the rat developmental studies) and a slight increase in fetal and litter incidence of gnarled forepaw(s). An increase in incidence of unossified olecranon and sternebrae was noted in the low- and mid-dose groups. **The developmental toxicity LOAEL is less than or equal to (≤) 4 mg/kg/day, based on the increased fetal and litter incidence of unossified olecranon and unossified sternebrae. The developmental toxicity NOAEL was not established (< 4 mg/kg/day)**.

The study is classified **Core-Supplementary** and does not satisfy the guideline requirement (OPPTS 870.3700) for developmental toxicity (teratology) study in rabbits, due to the lack of a NOAEL for developmental toxicity. In addition, in the study, the fetuses were incubated at approximately 34°C for approximately 24 hours. A record of survival was kept over that period. Following incubation all fetuses in each litter were fixed in alcohol and examined for internal abnormalities. This is a procedure that is different from the current guideline requirement for a developmental toxicity (teratology) study in rabbits. However, this study is considered an

acceptable study for maternal effects and can be used for risk assessment purposes, despite its limitation in developmental effects.

(2) In the developmental toxicity study (MRID 47242202), diiodomethyl p-tolyl sulfone (97.7% ± 0.1% a.i.; batch/lot PB1631LA01) was administered to 26 rabbits/dose by gavage at dose levels of 0, 0.05, 0.5, or 2.0 mg/kg bw/day from days 7 through 27 of gestation.

Maternal toxicity was observed at 2 mg/kg/day, including slightly increased absolute and relative thyroid weights. An increased incidence of very slight thyroid follicular dilatation was also noted, which was consistent with iodine toxicity, likely due to the high iodine content (60% by weight) of diiodomethyl p-tolyl sulfone. All the maternal effects are not toxicologically significant. **The maternal NOAEL is 2 mg/kg bw/day.**

No signs of developmental toxicity were observed at any dose level. **The developmental NOAEL is 2.0 mg/kg bw/day**, and the developmental LOAEL was not established**.**

The developmental toxicity study in the rabbit is classified **Acceptable/Guideline** and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700) in rabbits.

(3) In a range-finding developmental toxicity study (MRID 47214601), diiodomethyl p-tolyl sulfone (97.7% ± 0.1% a.i.; batch/lot PB1631LA01) was administered to 7 New Zealand White rabbits/dose by gavage at dose levels of 0, 1, 4, 8, or 15 mg/kg bw/day from days 7 through 27 of gestation.

Maternal toxicity was evidenced, at all tested dose levels, by increases in absolute and relative thyroid gland weights with corresponding thyroid follicle dilatation (slight to moderate) and distension with colloid. No appreciable follicular cell hyperplasia or hypertrophy was noted. One rabbit in each of the high-dose groups (8 and 15 mg/kg/day) aborted (GD 23, 24) following a period of decreased feed consumption, feces production, and body weight gain.

There was higher incidence of post-implantation loss in the two high-dose groups of 8 and 15 mg/kg/day (26.4% and 20.6%, respectively vs. 4.6% in control), which corresponded with increases in resorptions per litter and litters with resorptions, and decreases in litter size. There were no treatment-related developmental effects at 1 or 4 mg/kg/day. Both the maternal thyroid effects and the increases in post-implantation loss are consistent with iodine toxicity, most likely due to the iodine moieties of diiodomethyl p-tolyl sulfone. The agency will reach a final conclusion after a comprehensive review of the study.

Reproductive Toxicity

Adequacy of Database for Reproductive Toxicity: The database for reproductive toxicity is considered adequate. There are two reproductive toxicity studies (one-generation and two-generation) in rats in the agency's hazard database. A brief summary of each of the studies is provided below.

870.3800 Reproduction and Fertility Effects

(1) In an one-generation reproductive toxicity study in rats (MRID 46913302), diiodomethyl p-tolyl sulfone (97.4%; Lot # PB1631LA01) was administered in the diet to 30 Sprague-Dawley (Crl:CD [SD] IGS BR) rats/sex/dose group, at dietary levels of 0, 20, 80, or 200 mg/kg/day (adjusted time-weighted average of 0/0, 21.8/20.7, 86.1/82.0, or 213.9/204.0 mg/kg/day in males/females, respectively), for approximately ten weeks prior to mating to produce the F1 litters. This study was originally designed as a two-generation reproductive toxicity study, but was terminated during F1 littering due to high mortality in pups of the two highest treatment groups.

Signs of toxicity occurred at all dose levels in the parental generation. Low-dose females exhibited treatment-related perinasal soiling**.** Toxic effects observed in the mid-dose group included the following: decreased food consumption and body weights in males and females; increased mortality in females; increased incidence of pale skin/mucous membranes and perinasal soiling in females; decreased feces, and palpebral closure in females. At the high-dose level, decreased food consumption and body weights in males and females was observed, as well as an increased mortality in females.

Serum T3 (triiodothyronine) was decreased significantly ($p \leq 0.05$) by 26%, and TSH (thyroid stimulating hormone) was increased significantly ($p \leq 0.05$) by 98% compared to the surrogate controls. Grossly, diffuse roughened surface of the non-glandular mucosa of the stomach was observed, and additional treatment-related, non-specific findings of multifocal erosion/ulcer of the glandular mucosa of the stomach, decreased amount of fat, and decreased ingesta were noted. The following microscopic findings were also observed: (i) very slight chromophobe hypertrophy of the pars distalis of the pituitary gland; (ii) very slight to slight multifocal metaplasia of the intralobular duct of the salivary gland; (iii) very slight to slight diffuse hyperplasia of the non-glandular mucosa of the stomach; (iv) very slight altered tinctorial properties of the colloid of the thyroid gland; (v) very slight dilatation of the follicle of the thyroid gland; and (vi) very slight hypertrophy of the follicular cell of the thyroid gland.

The **parental systemic NOAEL could not be established** as all dose levels showed toxic effects. The **parental systemic LOAEL** is **20 mg/kg/day (adjusted time-weighted average of 21.8/20.7 mg/kg/day in males/females)**, based on decreased body weights, body weight gains, and food consumption in the males and clinical signs of toxicity (red perinasal soiling that occurred around parturition in the females).

The **offspring LOAEL is 20 mg/kg bw/day**, based on decreased body weights at all levels. The **offspring NOAEL could not be established**.

The **reproductive LOAEL is 80 mg/kg bw/day in females**, based on decreased gestation survival index. The **reproductive NOAEL is 20 mg/kg bw/day in females.** There were no treatment-related toxic effects in males at any dose level, so a reproductive LOAEL for males cannot be calculated.

Many of the effects observed were due to iodine toxicity since diiodomethyl p-tolyl sulfone is 60% iodine by weight. Consequently, a subsequent 2-generation study was conducted, using

more appropriate dose levels (MRID 46913301). This study instead became the basis for dose selection in the two-generation reproduction toxicity study.

This study is **UNACCEPTABLE/GUIDELINE** and does not satisfy the guideline requirement for a 2-generation reproductive study (OPPTS 870.3800, OECD 416) in rats due to the high mortality and iodine toxicity. A subsequent 2-generation study was conducted, using more appropriate dose levels; therefore, this study can be used as a dose-range finding study.

(2) In a two-generation reproductive toxicity study in rats (MRID 46913301), diiodomethyl p-tolyl sulfone (97.4% a.i.; Lot # PB1631LA01) was administered to 30 Sprague Dawley rats/sex/group at dietary levels of 0, 2.5, 10, or 40 mg a.i./kg/day for two successive generations. The P generation animals were fed the test diets for approximately 10 weeks prior to mating to produce the F1 litters. All litters were weaned on PND 21, and one F1 weanling/sex/litter was randomly selected to be a parent of the next generation, following the same procedures described for the first generation (treated for 10 weeks prior to mating beginning at weaning).

There were two treatment-related mortalities (one high-dose P and one high-dose F_1 adult female), although a total of 7 animals died during the study. Decreased body weight occurred in high-dose males from both generations due to decreased food consumption. F_1 females had low body weights beginning at birth through 34 days after weaning. P females had lower body weights sporadically during gestation and lactation, but F_1 females had a consistently lower body weight through gestation and lactation mainly due to the low body weight gains during gestation.

There was a dose-dependent significant increase in absolute and relative thyroid weights in male rats of both generations and in P female rats (mid- and high-dose) and F1 (high-dose; NS). This was accompanied by microscopic lesions in the thyroid (altered staining of the colloid in the follicle, hypertrophy, hyperplasia and/or follicular dilatation, consistent with hypothyroidism) observed at all doses in both sexes in both generations, males were generally more affected than females. Relative weights of the pituitary gland were increased for all treated P males and F_1 mid- and high-dose males. Absolute and relative weights of the pituitary gland were increased for all treated F_1 females; microscopic lesions (hypertrophy and hyperplasia of the chromophobe cells of the pars distalis of the anterior pituitary) were observed in high-dose animals (lower doses not examined).

There was a significant increase in relative salivary gland weights in P males. This is considered treatment-related as it had been noted in previous studies, but is considered of minor toxicological significance due to the lack of histopathological findings. This increase was not noted in the F_1 males or in females from either generation.
Absolute testes weights and epididymal weights were significantly decreased for all treated F_1 males, at a greater degree for the mid- and high-dose groups, with total sperm per epididymis decreased at both the mid- and high-dose levels and total sperm per testis decreased at the high dose. Relative testes weights of the high-dose F_1 males were decreased significantly. These weight changes of the testes and epididymis are considered to be treatment-related, although their toxicological significance and causation are not quite clear yet.

The **parental systemic LOAEL is 2.5 mg/kg bw/day**, based on thyroid weight increases and thyroid histopathology changes in males and females. The **parental systemic NOAEL could not be established** because effects on the thyroid were observed in both genders at every dose level.

There was a decrease in offspring survival in the high-dose group as measured by significant increases in post-implantation loss and decreases in live birth index and viability index for both generations. There was also a decrease in lactation index that was outside the historical control range. In the F_2 generation, there was also a decrease in survival in the mid-dose group. The decrease in live birth index, viability index, and lactation index did not reach statistical significance, but was outside the historical control range and is considered treatment-related. Body weights were reduced in the high-dose offspring from both generations. Gross and microscopic evaluation indicated an increase in the incidence of dilation of the renal pelvis in high-dose offspring of both generations.

The **offspring LOAEL is 10 mg/kg bw/day**, based on decreased offspring survival at this level. The **offspring NOAEL is 2.5 mg/kg bw/day**.

The mating indices for F_1 males and females were lower in the high-dose compared to the controls. While the decrease was not statistically significant, it was outside of the historical control range and is considered treatment-related. High-dose F_1 adult males had a decrease in absolute and relative testes weight that correlated with a decreased total sperm count in the testes and epididymis (only absolute epididymis weights were decreased). However, when measured on a gram of tissue basis, the sperm counts were similar to the control.

The **reproductive LOAEL is 40 mg/kg bw/day in males and females**, based on a biologically significant decrease in male and female mating indices, female conception index, and male and female fertility indices. The **reproductive NOAEL is 10 mg/kg bw/day in males and females**.

This study is **ACCEPTABLE/GUIDELINE** and satisfies the guideline requirement for a two-generation reproductive study (OPPTS 870.3800); OECD 416 in rats.

Chronic Toxicity/Carcinogenicity

Adequacy of Database for Chronic Toxicity/Carcinogenicity: There are no (combined) chronic toxicity/carcinogenicity studies in the agency's hazard database. These studies are anticipated to be required for registration review risk assessment. Based on the currently registered uses for diiodomethyl p-tolyl sulfone, the agency is anticipated to conduct a drinking water assessment for registration review, which may trigger the requirement of chronic toxicity/carcinogenicity studies, for adequately assessing the risk associated with the registered uses of diiodomethyl p-tolyl sulfone.

Mutagenicity

Adequacy of Database for Mutagenicity: The database for mutagenicity is considered adequate for the currently registered uses. Several mutagenicity studies, including *in vitro* and *in vivo*

studies, have been submitted and reviewed by the Office of Pesticide Programs (OPP). Diiodomethyl p-tolyl sulfone is found to be non-mutagenic. The summaries of these studies are provided below.

Gene Mutation

(1) In a bacterial reverse mutation assay (MRID 47307306), following a range-finding toxicity testing with *S. typhimurium* tester strain TA 100 and *E. coli* tester strain WP2*uvr*A in doses ranging from 10.0 to 5000 µg/plate (duplicate, with/without S9 mix), diiodomethyl p-tolyl sulfone (97.4% a.i.; Lot No. PB1631LA01) was administered, in triplicate, to cultures of *S. typhimurium* tester strains TA98, TA100, TA1535, and TA1537 and *E. coli* tester strain WP2*uvr*A at dose levels of 5.0, 10.0, 25.0, 50.0, 100, 250, and 500 µg/plate for all tester strains in the presence of S9 mix. In the absence of S9 mix, dose levels were 0.5, 1.0, 2.5, 5.0, 10, 25, and 50 µg/plate for the *S. typhimurium* tester strains and 2.5, 5.0, 10, 25, 50, 100, and 250 µg/plate with *E. coli* tester strain WP2*uvr*A for the initial assay. The concentrations tested in the confirmatory assay with all *S. typhimurium* tester strains were 2.5, 5.0, 10, 25, 50, 100, and 250 µg/plate in the presence of S9 mix and 0.5, 1.0, 2.5, 5.0, 10, 25, and 50 µg/plate for the absence of S9 mix; the tested concentrations for *E. coli* tester strain WP2*uvr*A were 5.0, 10, 25, 50, 100, 250, and 500 µg/plate both in the presence and absence of S9 mix. "The results of the *Salmonella-Escherichia coli*/mammalian-microsome reverse mutation assay pre-incubation method with a confirmatory assay with AMICAL™ 48 indicate that under the condition of the study, the test article did not cause a positive increase in the mean number of revertants per plate with any of the tester strains either in the presence or absence of microsomal enzymes prepared from Aroclor™-induced rat liver (S9)." A final conclusion will be reached upon completion of the agency's comprehensive review.

(2) In a mouse lymphoma forward mutation assay (MRIDs 00160070/94039011), the mouse lymphoma cell line, L5178Y $TK^{+/-}$, were exposed to diiodomethyl p-tolyl sulfone (99% a.i.; Lot # 66-207-CB) for four hours, in the absence and presence of rat liver S9 metabolic activation system. Diiodomethyl p-tolyl sulfone was assayed from 0.3 to 2.0 µg/ml (0.3, 0.5, 0.6, 0.8, 1.0, and 2.0 µg/ml) under the non-activation conditions; the highest concentration was excessive toxic. But the remaining five lower treatments caused low to moderate toxicity with no significant increased mutant frequency above the background. In the presence of S9 metabolic activation, the concentrations tested (ranged from 0.5 to 5.0 µg/ml) induced a wide range of toxicity; however, no significant increases in the mutant frequency were identified. Diiodomethyl p-tolyl sulfone did not demonstrate mutagenic potential in the mouse lymphoma assay.

This study is classified **Acceptable**.

Cytogenetics

(1) Diiodomethyl p-tolyl sulfone (96.5% a.i.; Lot # 3-0410) was administered to Chinese Hamster Ovary (CHO) cells cultures at dose levels of 0.125, 0.25, 0.5, 1, 2, and 4 µg/ml in the non-activated study and at 0.5, 1, 2, 4, 8, and 16 µg/ml in the S-9 activated study (MRID

43120601). At the highest doses, there were sufficient indications of a cytotoxic response (reduction in mitotic index). Under the condition of this assay, there was no indication of a positive clastogenic and/or aneugenic response in the absence (harvested at 18 hours) or S-9 activation (harvested at 12 hours). Diiodomethyl p-tolyl sulfone (Amical® 48 Preservative) was concluded to be negative in the chromosome aberrations in Chinese Hamster Ovary cells (CHO) cells cytogenetics assay.

This study is classified **Acceptable/Non-guideline** and satisfies the Guideline requirement for a structural chromatic aberration assay (OCSPP 870.5375).

(2) In an *in vivo* mouse micronucleus assay (MRIDs 00160071), diiodomethyl p-tolyl sulfone (99% a.i.; Lot # 66-207-CB) was administered, at concentrations of 0.5, 2.5, and 5.0 g/kg (based on an oral LD_{50}), to 5 ICR mice/sex/group intraperitoneally (i.p.) by individual weight with volumes based on 10 ml/kg. Animals were dosed on an acute regimen with groups killed 24, 48, and 72 hours post-dosing. The negative and positive control groups were killed 24 hours after dosing. An additional group of 5 mice/sex were treated with 5.0 g/kg dose concentration and were only used to replace animals which died in the primary dose groups. Bone marrow cells were harvested at the sacrificing schedule stated above (24, 48, and 72-hours post-treatment). The positive control was triethylenemelamine (TEM) used at 1.5 mg/kg, administered by one i.p. injection. Diiodomethyl p-tolyl sulfone did not induce toxic signs in any animals, nor did positive or negative controls.

No significant increases in number of micronucleated polychromatic erythrocytes (MN-PCEs) frequencies were reported in any dose group over the negative control animals, whereas a significant increase in the frequencies of MN-PCEs was observed in the positive control group. The mean percent PCE values were significantly reduced at 500 mg/kg and for the positive control groups compared to the corresponding negative controls. Diiodomethyl p-tolyl sulfone did not demonstrate mutagenic potential in the mouse bone marrow micronucleus assay under the test condition.

This study is classified **Acceptable**.

Other Genotoxicity

(1) In an *in vitro* primary rat hepatocyte unscheduled DNA synthesis (UDS) assay (MRIDs 00160072/94039012), fresh hepatocytes from rat liver were exposed to diiodomethyl p-tolyl sulfone (99% a.i.; Lot # 66-207-CB) at concentrations ranged from 0.052 to 5.19 µg/mL. The positive control used was a-acetylaminofluorene (2-AAF) at 0.05 and 0.10 µg/mL; the test material solvent served as the negative control.
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No significant increases in mean net nuclear grains (NNG), or in the percent of nuclei with six or more net grains, were reported at any dose level at any time point. This was comparable to the solvent controls. There was no evidence of induction of unscheduled DNA synthesis in rat primary hepatocytes over the background. The positive control elicited a clear positive response. It was concluded that, under the condition of the present test, diiodomethyl p-tolyl sulfone did

not demonstrate mutagenic potential in the present *in vitro* primary rat hepatocyte unscheduled DNA synthesis (UDS) assay.

This study is classified **Acceptable**.

Neurotoxicity

870.6200 Neurotoxicity Screening Battery

Adequacy of Database for Neurotoxicity: The database for neurotoxicity is considered incomplete. There are no neurotoxicity studies in the agency's hazard database. A neurotoxicity screening battery is anticipated to be required for registration review risk assessment, based on the currently registered uses for DIMTS.

Immunotoxicity

870.7800 Immunotoxicity Study

Adequacy of Database for Immunotoxicity: The database for immunotoxicity is considered incomplete. There are no immunotoxicity studies in the agency's hazard database. An immunotoxicity study is anticipated to be required for registration review risk assessment, based on the currently registered uses for diiodomethyl p-tolyl sulfone.

Other Toxicological Effects

Metabolism and Pharmacokinetics

In a metabolism study (MRID 47076601), Amical^{TM} 48 Antifungal Agent (1-((diiodomethyl)sulpfonyl)-4-methyl benzene,; 97.7% a.i., Lot no. 172-015-032) and ^{14}C-Amical methyl substituted to the aromatic ring was radiolabeled; 99.8% a.i., Lot no. PB1631LA01) was administered to Fisher 344 or Sprague-Dawley rats following the exposure schemes described below. Five oral absorption, distribution, and elimination studies in F-344 rats were performed each using 4 rats/sex/dose at target dose levels of 5.0 or 50 mg/kg. In these studies a single oral dose was administered via gavage at calculated doses of 5.0 mg/kg (Groups 1, 3, and 5; actual concentrations were for Group 1, 5.03 mg/kg in males and 5.02 females; Group 3, 5.26 mg/kg in males and 5.14 females; Group 5, 5.06 mg/kg in males and 5.13 females) or 50 mg/kg (Groups 2 and 4; actual concentrations were for Group 2, 51.44 mg/kg in males and 51.19 mg/kg in females; Group 4, 51.09 mg/kg in males and 51.99 mg/kg in females). In a multi-dosing study, animals were administered 5.0 mg/kg unlabeled Amical^{TM} 48 (actual concentration was not determined for unlabeled Amical^{TM} 48) via the diet for 14 days, then dosed with a comparable single oral dose of radiolabeled Amical^{TM} 48 via gavage (Group 6; actual concentrations were 5.10 mg/kg in males and 4.96 mg/kg in females). A single 6 hour dermal dose was utilized with both males and females (Group 8) receiving 5.0 mg/kg ^{14}C-Amical^{TM} 48, the actual measure doses were 6.99 mg/kg in males and 9.14 mg/kg in females; volatility studies showed that

ambient temperatures did not cause dermal doses of Amical^{TM} 48 to dissipate. A single oral dose of 5.0 mg/kg ^{14}C- Amical^{TM} 48 (actual concentration 5.04 mg/kg) was given to 4 Sprague-Dawley females (Group 7). Metabolite distribution was determined in Groups 1, 2, 5, 7, and 8 (Group 8 excreta had metabolite concentrations too low to analyze) from urine and plasma; free iodine was determined in all Groups. Pharmacokinetic parameters were determined in Groups 1, 2, 7, and 8.

After a single oral dose of 5.0 or 50 mg/kg ^{14}C-Amical^{TM} 48, the maximum concentration of Amical^{TM} 48 (C_{max}) in the blood is reached within an 15 minutes at the low dose and 30 minutes for the high dose, and the plasma half-life at the low doses were between 1-2 hours and a 2-fold increase was noted at the high dose with a plasma half-life of 2-4 hours; oral dose was available in a dose proportionate manner. Plasma radioactivity levels were non-detectible after 24 hours except in the high-dose males that were non-detectable the next day, this coincides with higher levels of glutathione conjugated parent compound observed in the males. Free iodine elimination was slower than the rapid elimination of the radiolabeled Amical^{TM} 48 equivalent; the half-life of free iodine was approximately 2.5 hours in the low oral doses and 4-5 hours in the high oral dosed F344 rats. No difference in absorption, route of elimination, or pharmacokinetics were observed when comparing F344 rats and Sprague-Dawley rats; however, the Sprague-Dawley rats displayed a decreased elimination of free iodine, with a plasma half-life of 7 hours, a 3 fold increase over the F344 rats dosed at the same rate of 5 mg/kg. The maximum concentration (C_{max}) and time to maximum concentration (t_{max}) was the same in F344 and Sprague-Dawley rats, but the area under the curve (AUC) and half-life ($t_{1/2}$) were longer suggesting greater bioavailability of iodine in the Sprague-Dawley rats. Radioactivity elimination in Sprague-Dawley rats was comparable to F344 rats.

After multiple doses of unlabeled Amical^{TM} 48, one dose of radioactive Amical^{TM} 48 displayed no difference in absorption, elimination, pharmacokinetics, metabolism, or route of elimination. Dermal Amical^{TM} 48 was absorbed 7-10% of the applied dose; plasma radioactivity and iodine were negligible, 5-7% were found in the urine and fecal elimination was <0.3%. The dermal dose was slowly absorbed and rapidly eliminated mainly in the urine with 23-30% of the absorbed dose in the urine after 24 hours and 38-45% after 48 hours. The dermal application site wash was the major depot of radioactivity with 80% rinsed off the males and 90% in females. The application site had 1.1 and 2.4% of the applied dose, in males and females, respectively; stratum conrneum (tape strips) had 0.1-0.2% of the applied dose. Tissues had 0.3% of the applied dose or 3-5% of the absorbed dose at the end of the study. Recoveries were between 90-97%.

The major route of elimination was through the urine for all exposure methods with 87-97% excreted and most was within the first six hours (78-92%); elimination in the feces accounted for 7-13% of the radioactivity. Organ/tissue radioactivity levels were <1% of the dose received after 7 days, this also included the plasma. Results indicate that orally administered Amical^{TM} 48 is rapidly and almost completely absorbed from the gastro-intestinal tract and eliminated quickly. Expired air and volatiles was not a major route of elimination, negligible findings were noted in all air traps.

Distribution patterns in the orally dosed animals were similar between the single- and repeat-dosed Groups with the highest residual radioactivity found in the major elimination organs/tissue, i.e., the kidney, liver, and plasma; however, the levels were low. No organ

demonstrated accumulation of Amical^{TM} 48 with highest levels of Amical^{TM} 48 equivalent in the plasma 7 days after dosing. The plasma, kidney, and liver eliminates Amical^{TM} 48 equivalent rapidly with most of the concentration eliminated by the 6th hour.

Upon absorption, iodine is liberated from the Amical^{TM} 48 reaching maximum concentration at 4 hours in the low-dose groups and 2 hours in the high-dose groups. Elimination of iodine is slower than the radioactive portion of Amical^{TM} 48, with 9-13% of free iodine in the urine and 5-7% of the radioactivity in the urine. The total free iodine detected in the urine was 59-73% and 41-43% of the total radioactivity, in low- and high-dose groups, respectively. Fecal iodine elimination was between 7-13% and most was within the first 24 hours. Dermal exposures produced an iodine profile in the urine that was different than oral exposures; the total amount of iodine in the urine was higher than oral exposure groups, indicating a higher metabolism of one or both of the iodine groups from DIMTS.

In the blood and excreta analyzed for metabolites, no parent compound was found. The major metabolites were the parent conjugated with glucuronide and 3 non-parent oxidated benzylic methyl moiety or minor ring hydroxylation. Two major metabolites in the blood, in order of concentration, were p-iodomethylsulphone benzoic acid and p-methylsulfone benzoic acid. Major metabolites in the urine for the low-dose group, in order of concentration, were p-methylsulfone benzoic acid, p-iodomethylsulphone benzoic acid, and methyl-p-tolylsulpfone, which accounted for 62-88% of the dose; whereas, p-iodomethylsulphone benzoic acid, p-methylsulfone benzoic acid, and methyl-p-tolylsulpfone (in order of concentration), which accounted for 75-88% of the dose, were the major metabolites in the urine for the high-dose group. Major fecal metabolites were p-methylsulfone benzoic acid and p-iodomethylsulphone benzoic acid, which accounted for 5-9% of the dose.

This metabolism study in the rat is classified **ACCEPTABLE/GUIDELINE** and satisfies the guideline requirement for a metabolism study (OPPTS 870.7485; OECD 417) in rats.

Dermal Penetration Study

There is no acceptable guideline dermal penetration study. There is some dermal absorption information in the pharmacokinetics and metabolism study (MRID 47076601) summarized above.

In the pharmacokinetics and metabolism study (MRID 47076601), 4 Fischer 344 rats/sex (Group 8) dermally received a single dose of ^{14}C-diiodomethyl p-tolyl sulfone on the shaved back (between scapula). The application site was covered with mesh and was washed 6 hours after application. Dose suspension for the dermal application was prepared at the target concentration of ~ 8.8 mg/ml and applied at a dose volume of 10 µl/cm^2 to 12 cm^2, which resulted in a dose of ~ 5 mg/kg (the actual measure doses were 6.99/9.14 mg/kg in males/females). Volatility studies showed that ambient temperatures did not cause dermal doses of ^{14}C-diiodomethyl p-tolyl sulfone to dissipate. Absorption of the dermally applied diiodomethyl p-tolyl sulfone was 7-12% of the dose. The dermally applied dose was slowly absorbed from the site of application and rapidly eliminated in urine accounting for 23-30% and 38-45% of the absorbed dose within 24 hours and 48 hours, respectively. Between 5 and 7% of the applied dose was excreted in urine, fecal elimination was negligible (~0.3%). The level of radioactivity and free iodide in the plasma

of the dermally dosed animals remained below the level of quantification (< LOQ) throughout the study. The total amount of iodide found in the urine of the dermally dosed rats was 10-40% higher than the total radioactivity, which was opposite to what was observed in the orally dosed animals, indicating higher metabolism/liberation of one or both of the iodide from the parent molecule. Elimination of radioactivity and iodide in urine continued during the analysis period due to slow continuous absorption of ^{14}C-diiodomethyl p-tolyl sulfone from the application site. It is anticipated to have variations ranging from 90-110% recovery rates for the dermal absorption study. Therefore, the agency concluded that the appropriate dermal absorption factor in the risk assessment should be approximately 10%.

Table A2 – Toxicity Profile for DIMTS

Guideline No./ Study Type	MRID No./ Study Classification	Dosing and Animal Information	Results
Subchronic Toxicity			
870.3100 90-day Oral (Rat)	MRID 42054402/43246401 Core-Minimum	Purity 95% Crl:CD(SD)BR rats (10/sex/dose) 0, 5, 20, or 80 (15/sex) mg/kg/d, in diet, for 90-94 days.	**NOAEL ≥ 80 mg/kg/d** The only significant findings in the treated animals were statistically significant elevations in mean phosphorus and cholesterol levels in the high dose group males and squamous metaplasia of the salivary gland ducts in three males in the high dose group. All of the effects noticed in the treatment groups were not considered toxicologically significant. The highest dose does not reach the maximum tolerated dose (MTD).
870.3100 90-day Oral (Rat)	MRID 47338201 Under agency review	Purity 97.4% Sprague-Dawley (CD) (8 rats/sex/dose) 0, 5, 20, 100, or 250 mg/kg/d, in diet, for at least 13 weeks	The study author concluded: **NOAEL = 20 mg/kg/d**, based on hyperplasia of the non-glandular mucosa of the stomach and squamous metaplasia of the salivary glands at 100 mg/kg/d
870.3150 90-day Oral (Dog)	MRID 42054403/43246402 Core-Minimum	Purity 95% Beagle dogs (4/sex/group) 0, 2, 10, or 60 mg/kg/day, in gelatin capsules, for 96-100 days	**NOAEL = 2 mg/kg/day** **LOAEL = 10 mg/kg/day**, based on histopathological changes observed in the thyroid glands (degeneration of the thyroid gland [mineralization within colloid clumping of sloughed follicular cells and colloid depletion]), salivary gland (Sialadenitis [ductal and periductal inflammation of the salivary gland]) and gastrointestinal (GI) tract (hemorrhagic gastritis, necrosis of the small intestine and keratitis).

Guideline No./ Study Type	MRID No./ Study Classification	Dosing and Animal Information	Results
870.3200 21/28 day dermal (rats)	MRID 48236901 Acceptable/Guideline	Purity 94.6% Crl:CD(SD)BR rats (10/sex/dose) 0, 20, 100, or 500 mg/kg/day, semi-occlusion, 6 hr/day, 7 days/wk, for 28 consecutive days.	**$NOAEL_{systemic}$ = 20 mg/kg/day (♀)** and **not established for males** **$LOAEL_{systemic}$ = 100 mg/kg/day (♀)**, based on thyroid effects (very slight hypertrophy of thyroid follicular epithelial cells and altered tinctorial properties of the colloid, characterized by the presence of pale to very pale eosinophilic colloid in the follicles). **$NOAEL_{dermal}$ = 20 mg/kg/day** **$LOAEL_{dermal}$ = 100 mg/kg/day**, based on multifocal scabs, slight epidermal hyperplasia (acanthosis) with very slight parakeratosis, and very slight multifocal subacute to chronic inflammation in the dermis.
870.3465 90-day inhalation Subchronic (Rat)	MRID 48264901 Acceptable/Guideline	Purity 97.3% Crl:CD(SD) rats (10/sex/concentration) 0, 1, 7, or 30 mg/m^3, nose only, 6 hr/d, 5 days/wk, for 13 wks (65 total exp. days). The average mass median aerodynamic diameter (MMAD) of the test material aerosol was 2.6, 2.7, and 2.6 µm for exposure concentration groups 1, 7, and 30 mg/m^3, respectively.	**NOAEC = 1 mg/m^3** **LOAEC = 7 mg/m^3**, based on treatment-related systemic effects were observed in the thyroid glands (colloid with altered tinctorial properties) and unilateral or bilateral parakeratosis with inflammation in the anterior nasal cavity in both male and female rats.
Developmental Toxicity			
870.3700a Developmental Toxicity (Rat)	MRIDs 42054404/42054405/ 43246403 Core-Guideline	Purity 95% Crl:CD(SD) albino rats (22/group) 0, 100, 300, or 1000 mg/kg/day, oral gavage, gestation days (GD) 6-15 For MRID 42054405: Crl:CD(SD) albino rats (25/group) 0 or 1000 mg/kg/day, oral gavage, gestation days (GD) 6-15	**$NOAEL_{maternal}$ = 100 mg/kg/d** **$LOAEL_{maternal}$ = 300 mg/kg/d**, based on ↓ body weight gain and food consumption. **$NOAEL_{developmental}$ = 300 mg/kg/d** **$LOAEL_{developmental}$ = 1000 mg/kg/d**, based on ↓ mean litter size, ↑ number of resorptions relative to the number of implantation sites, ↓ mean fetal body weight, ↑ incidences of umbilical hernia, and incomplete ossification of the supraoccipital bones.

Guideline No./ Study Type	MRID No./ Study Classification	Dosing and Animal Information	Results
870.3700a Developmental Toxicity (Rat)	MRIDs 47373805 Under agency review	Purity > 95% Wistar rats (22/group) 0, 0.125, 0.25, 0.5, or 1.0% (estimated daily intakes of test material 0, 100, 182, 288, or 411 mg/kg/d, respectively), in the diet, gestation days (GD) 6-15	Significant lower maternal body weight gain and food consumption were observed in the three higher dose groups. No significant changes induced by the test substance were detected in the numbers of resorption, fetal death, or body weight of live fetuses. No evidence of teratogenesis was revealed in fetuses during morphological examination.
870.3700b Developmental Toxicity (Rabbit)	MRIDs 42243801/43246404 Core-Supplementary	Purity 95% Pregnant New Zealand White rabbits 0, 4, 15, or 60 mg/kg/day, oral gavage, gestation day (GD) 6-18, inclusive	**$NOAEL_{maternal}$ = 4 mg/kg/d** **$LOAEL_{maternal}$ = 15 mg/kg/d**, based on clinical signs (deaths) and ↓ body weight gain and food consumption **$NOAEL_{developmental}$ < 4 mg/kg/d (not established)** **$LOAEL_{developmental}$ ≤ 4 mg/kg/d**, based on increased fetal and litter incidence of unossified olecranon and unossified sternebrae
870.3700b Developmental Toxicity (Rabbit)	MRID 47242202 Acceptable/Guideline	Purity 97.7% 26 rabbits/dose 0, 0.05, 0.5, or 2.0 mg/kg/day, gavage, gestation days (GD) 7-27	**$NOAEL_{maternal}$ = 2 mg/kg/d** (HDT) **$LOAEL_{maternal}$** not established. **$NOAEL_{developmental}$ = 2 mg/kg/d** (HDT) **$LOAEL_{developmental}$** not established.
870.3700b Developmental Toxicity (Rabbit)	MRIDs 47214601 Under agency review	Purity 97.7% New Zealand White rabbits (7/dose) 0, 1, 4, 8, or 15 mg/kg/day, gavage, gestation days 7-27	**$NOAEL_{maternal}$ < 1 mg/kg/d** (LDT) **$LOAEL_{maternal}$ = 1 mg/kg/d**, based on ↑ in absolute and relative thyroid gland weights with corresponding thyroid follicle dilatation (slight to moderate) and distension with colloid at all tested dose levels. **$NOAEL_{developmental}$ = 4 mg/kg/d** (HDT) **$LOAEL_{developmental}$ = 8 mg/kg/d**, based on higher incidence of post-implantation loss (26.4% and 20.6%, respectively vs. 4.6% in control), which corresponded with increases in resorptions per litter and litters with resorptions, and decreases in litter size. The agency will reach a final conclusion after a comprehensive review of the study.
Reproduction Toxicity			

Guideline No./ Study Type	MRID No./ Study Classification	Dosing and Animal Information	Results
870.3800 Reproduction	MRID 46913302 Unacceptable/Guideline	Purity 97.4% Sprague-Dawley Crl:CD [SD] IGS BR rats (30/sex/dose group) 0, 20, 80, or 200 mg/kg/day (adjusted time-weighted average of 0/0, 21.8/20.7, 86.1/82.0, or 213.9/204.0 mg/kg/day in males/females, respectively), in diet, for approximately ten weeks prior to mating to produce the F1 litters. This study was originally designed as a two-generation reproductive toxicity study, but was terminated during F1 littering due to high mortality in pups of the two highest treatment groups.	**$NOAEL_{parental}$ < 5 mg/kg/d** (not established) **$LOAEL_{parental}$ = 20 mg/kg/d (adjusted time-weighted average of 21.8/20.7 mg/kg/day in males/females)**, based on decreased body weights, body weight gains, and food consumption in the males and clinical signs of toxicity (red perinasal soiling that occurred around parturition in the females). **$NOAEL_{offspring}$ < 20 mg/kg/d** (not established); **$LOAEL_{offspring}$ = 20 mg/kg/d**, based on decreased body weights at all levels. **$NOAEL_{reproductive}$ = 20 mg/kg/d (♀)** **$LOAEL_{reproductive}$ = 80 mg/kg/d (♀)**, based on decreased gestation survival index. There were no treatment-related toxic effects in males at any dose level, so a reproductive LOAEL for males cannot be calculated
870.3800 Reproduction	MRID 46913301 Acceptable/Guideline	Purity 97.4% Sprague Dawley rats (30/sex/group) 0, 2.5, 10, or 40 mg a.i./kg/day, in diet, for two successive generations (P: approx. 10 weeks prior to mating to produce the F1 litters. All litters were weaned on PND 21, and one F1 weanling/sex/litter was randomly selected to be a parent of the next generation and treated for 10 weeks prior to mating beginning at weaning).	**$NOAEL_{parental}$** < 2.5 mg/kg/d (not established) **$LOAEL_{parental}$ =** 2.5 mg/kg/d, based on ↑ thyroid weight increases and thyroid histopathology changes in males and females at every dose level. **$NOAEL_{offspring}$ = 2.5 mg/kgd** **$LOAEL_{offspring}$ = 10 mg/kg/d**, based on decreased offspring survival. **$NOAEL_{reproductive}$ = 10 mg/kg/d** **$LOAEL_{reproductive}$ = 40 mg/kg/d**, based on a biologically significant ↓ in male and female mating indices, female conception index, and male and female fertility indices.
Chronic Toxicity			
870.4100 Chronic Toxicity	A chronic toxicity study is not available for DIMTS.		
Carcinogenicity			
870.4200 Carcinogenicity	A carcinogenicity study is not available for DIMTS.		
Mutagenicity			

Guideline No./ Study Type	MRID No./ Study Classification	Dosing and Animal Information	Results
870.5100 Bacterial reverse mutation test	MRID 47307306 Under agency review	Purity 97.4% *S. typhimurium* TA98, TA100, TA1535, and TA1537 and *E. coli* WP2*uvr*A The initial assay: 5.0, 10.0, 25.0, 50.0, 100, 250, and 500 µg/plate for all tester strains (+S9); 0.5, 1.0, 2.5, 5.0, 10, 25, and 50 µg/plate for the *S. typhimurium* tester strains (- S9) and 2.5, 5.0, 10, 25, 50, 100, and 250 µg/plate with *E. coli* WP2*uvr*A (-S9) for. The confirmatory assay: *S. typhimurium* tester strains – 2.5, 5.0, 10, 25, 50, 100, and 250 µg/plate (+S9) and 0.5, 1.0, 2.5, 5.0, 10, 25, and 50 µg/plate (-S9) *E. coli* WP2*uvr*A – 5.0, 10, 25, 50, 100, 250, and 500 µg/plate (+/-S9)	The study author concluded that "The results of the *Salmonella-Escherichia coli*/mammalian-microsome reverse mutation assay pre-incubation method with a confirmatory assay with AMICAL™ 48 indicate that under the condition of the study, the test article did not cause a positive increase in the mean number of revertants per plate with any of the tester strains either in the presence or absence of microsomal enzymes prepared from Aroclor™-induced rat liver (S9)."
870.5300 Mammalian cell gene mutation test	MRIDs 00160070/94039011 Acceptable	Purity 99% mouse lymphoma cells (L5178Y $TK^{+/-}$) 0.3 – 2.0 µg/ml (0.3, 0.5, 0.6, 0.8, 1.0, and 2.0 µg/ml) (-S9) and 0.5 – 5.0 µg/ml (+S9), for a period of 4 hours	**Negative**
870.5300 Mammalian cell gene mutation test	MRID 43120601 Acceptable/Non-guideline	Purity 94.5% Chinese hamster ovary (CHO) cells 0.125, 0.25, 0.5, 1, 2, and 4 µg/ml (-S9) and 0.5, 1, 2, 4, 8, and 16 µg/ml (+S9)	**Negative**
870.5385 *In vivo* mouse micronucleus assay	MRID 00160071 Acceptable	Purity 99% ICR mice (5/sex/group) 0.5, 2.5, and 5.0 g/kg (based on an oral LD_{50}), intraperitoneally (i.p.), by individual weight with volumes based on 10 ml/kg. Animals were killed and bone marrow cells at 24, 48, and 72 hours post-dosing. The negative and positive control groups were killed 24 hours after dosing.	**Negative**

Guideline No./ Study Type	MRID No./ Study Classification	Dosing and Animal Information	Results
870.5550 (*In vitro*) Unscheduled DNA synthesis	MRIDs 00160072/94039012 Acceptable	Purity 99% Rat hepatocyte cells 0.052 to 5.19 µg/mL. The positive control used was a-acetylaminofluorene (2-AAF) at 0.05 and 0.10 µg/mL; the test material solvent served as the negative control	**Negative**
870.5550 Unscheduled DNA synthesis	MRID 41298503 Acceptable	Purity 81% Rat (male) hepatocyte cells $5x10^{-7}$ – $1x10^{-3}$ mL/mL	**Negative**
870.6200 Neurotoxicity screening battery	A neurotoxicity screening battery is not available.		
870.7800 Immunotoxicity	An immunotoxicity study is not available.		
Metabolism			

870.7485 Metabolism and Pharmacokinetics	MRID 47076601 Acceptable/Guideline	Purity 99.8% (radiolabeled); 97.7% (non-radiolabeled) Fisher 344 or Sprague-Dawley rats (4/dose group) Exposure schemes: - Single oral dose: 5.0 mg/kg ^{14}C-Amical™ 48 (actual conc. [♂/♀]: 5.03/5.02; 5.26/5.14; and 5.06/5.13 mg/kg for Groups 1, 3, and 5, respectively) or 50 mg/kg ^{14}C-Amical™ 48 (actual conc. [♂/♀]: 51.44/51.19 and 51.09/51.99 mg/kg for Groups 2 and 4, respectively), via gavage - Multiple oral doses (Group 6): 5.0 mg/kg unlabeled Amical™ 48 (actual conc. not determined), via the diet, for 14 days; then dosed with a comparable single oral dose of ^{14}C-Amical™ 48 via gavage (actual conc. [♂/♀]: 5.10/4.96 mg/kg); - Single dermal dose (Group 8): 5.0 mg/kg ^{14}C-Amical™ 48 (actual measure doses [♂/♀]: 6.99/9.14 mg/kg) for 6 hr; - Single oral dose (Group 7): 5.0 mg/kg ^{14}C-Amical™ 48 (actual conc.: 5.04 mg/kg) given to 4 Sprague-Dawley females Metabolite distribution was determined in Groups 1, 2, 5, 7, and 8 (Group 8 excreta had metabolite concentrations too low to analyze) from urine and plasma; free iodine was determined in all Groups. Pharmacokinetic parameters were determined in Groups 1, 2, 7, and 8.	After a single oral dose of 14C-Amical™ 48, the plasma concentrations peaked (Cmax) within15 minutes and 30 minutes for the low dose (5 mg/kg) and the high dose (50 mg/kg), respectively, and the plasma half-life at the low doses were between 1-2 hours and 2-4 hours (2-fold increase) at the high dose. Plasma radioactivity levels were non-detectible after 24 hours except in the high-dose males that were non-detectable the next day, this coincides with higher levels of glutathione conjugated parent compound observed in the males. Free iodine elimination was slower than the rapid elimination of the radiolabeled AmicalTM 48 equivalent; the half-life of free iodine was approximately 2.5 hours in the low oral doses and 4-5 hours in the high oral dosed F344 rats. No difference in absorption, route of elimination, or pharmacokinetics were observed when comparing F344 rats and Sprague-Dawley rats; however, the Sprague-Dawley rats displayed a decreased elimination of free iodine, with a plasma half-life of 7 hours, a 3 fold increase over the F344 rats dosed at the same rate of 5 mg/kg. The maximum concentration (Cmax) and time to maximum concentration (tmax) was the same in F344 and Sprague-Dawley rats, but the area under the curve (AUC) and half-life (t1/2) were longer, suggesting greater bioavailability of iodine in the Sprague-Dawley rats. Radioactivity elimination in Sprague-Dawley rats was comparable to F344 rats. After multiple doses of unlabeled AmicalTM 48, one dose of 14C-Amical™ 48 displayed no difference in absorption, elimination, pharmacokinetics, metabolism, or route of elimination. Dermal 14C-Amical™ was absorbed 7-10% of the applied dose; plasma radioactivity and iodine were negligible, 5-7% were found in the urine and fecal elimination was <0.3%. The dermal dose was slowly absorbed and rapidly eliminated mainly in the urine with 23-30% of the absorbed dose in the urine after 24 hours and 38-45% after 48 hours. The dermal application site wash was the major depot of radioactivity with 80% rinsed off the males and 90% in females. Tissues had 0.3% of the applied dose or 3-5% of the absorbed dose at the end of

			the study. Recoveries were between 90-97%. The major route of elimination was through the urine for all exposure methods with 87-97% excreted and most was within the first six hours (78-92%); elimination in the feces accounted for 7-13% of the radioactivity. Organ/tissue radioactivity levels were <1% of the dose received after 7 days, this also included the plasma. Results indicate that orally administered Amical™ 48 is rapidly and almost completely absorbed from the gastro-intestinal tract and eliminated quickly. Expired air and volatiles was not a major route of elimination. Distribution patterns in the orally dosed animals were similar between the single- and repeat-dosed Groups with the highest residual radioactivity found in the major elimination organs/tissue, i.e., the kidney, liver, and plasma; however, the levels were low. No organ demonstrated accumulation of Amical™ 48 with highest levels of Amical™ 48 equivalent in the plasma 7 days after dosing. The plasma, kidney, and liver eliminates Amical™ 48 equivalent rapidly with most of the concentration eliminated by the 6th hour. Upon absorption, iodine is liberated from the Amical™ 48 reaching maximum concentration at 4 hours in the low-dose groups and 2 hours in the high-dose groups. Elimination of iodine is slower than the radioactive portion of Amical™ 48, with 9-13% of free iodine in the urine and 5-7% of the radioactivity in the urine. The total free iodine detected in the urine was 59-73% and 41-43% of the total radioactivity, in low- and high-dose groups, respectively. Fecal iodine elimination was between 7-13% and most was within the first 24 hours. Dermal exposures produced an iodine profile in the urine that was different than oral exposures; the total amount of iodine in the urine was higher than oral exposure groups, indicating a higher metabolism of one or both of the iodine groups from Amical™ 48. ^{14}C-Amical™ 48 was highly metabolized. No parent compound was identified in the blood and excreta. The major metabolites were the parent conjugated with glucuronide and 3 non-

Guideline No./ Study Type	MRID No./ Study Classification	Dosing and Animal Information	Results
			parent oxidated benzylic methyl moiety or minor ring hydroxylation.

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Appendix B Environmental Fate

Environmental Fate and Transport Properties of DIMTS and its Degradation Products

Water and Sediment

Hydrolysis

DIMTS is stable to hydrolysis at pH 5, but degrades rapidly in pH 7 and 9 buffered solutions with linear half-lives of 2.1-3.6 days. The major degradate was MIMPTS, whose concentrations did not decline in the study and reached 90-100 % of applied by the end of the study. The minor degradates MPTS and PTSOA were formed in the study (MRID 43008701).

Aqueous Photolysis

DIMTS degraded with a half-life of 1.4 hours and no degradation occurred in the dark controls, which is consistent with the results of the hydrolysis study. Two significant degradates increased until the end of the study, including PTSOA which increased to 90 % by 24 hours, and MPTS, which increased to about 10 % (MRID 47343001).

Octanol-Water Partition Coefficient and Bioconcentration in Fish

The log P value for parent DIMTS (2.66) in Table 4 indicates that there is little potential for bioconcentration of fish, and the log P values for the degradation compounds (-0.62 to 2.3) in Table 5 also indicate little potential for bioconcentration of the degradation compounds.

Aerobic Aquatic Metabolism

Aerobic aquatic metabolism data have not been submitted but are not required because the results from the hydrolysis and aerobic soil studies both indicate that parent DIMTS degrades to the MIMPTS and MPTS degradates. Also, data on the persistence of DIMTS and MIMPTS under aquatic conditions are also available.

Anaerobic Aquatic Metabolism

Under anaerobic aquatic conditions, the total system, non-linear half-lives of parent DIMTS and the degradation compound MIMPTS were 9.6 and 11 days, respectively. Parent compound was associated more with water than sediment through 7 days and more in sediment afterwards. MIMPTS reached 16.2 % by 7 days, and then declined to <1 % by 3-6 months. MIMPTS was associated more in water than sediment for 60 days and then in equal portions thereafter. The degradation compound MPTS increased to 94.5 by 4-6 months, and was associated with water rather than sediment over the duration of the study. The degradation compound PTSOA did not reach significant levels in the study. Extractable residues were 23-31 % (0-14 days) and 16-18

% by 30-180 days, and non-extractable residues never exceeded 2 %. Water soluble residues ranged from 68 to 85 % and volatiles did not exceed 0.8 % (MRID 42177201).

Leaching from treated wood

In a submerged wood block study (E11-06, MRID 47375907), DIMTS leached from wood treated with 5.6-16 mg/cm^3 with maximum rates of 23.5-49.3 µg/cm^2/day and cumulative rates of 309-413 µg/cm^2. The percentages of leached DIMTS leached were 17.9 % for the 5.6 mg/cm^3 treatment rate, 9.9 for the 11.2 mg/cm^3 treatment rate, and and 8.1 % for the 16 mg/cm^3 treatment rates. Table B1 contains additional information on wood leaching.

Soil

Soil Leaching/Adsorption/Desorption Batch Equilibrium

Data on sorption of parent DIMTS to soil are required, along with the degradation products MIMPTS and MPTS are required because these compounds can be present in significant amounts (>10 %) in the environment based on the results of both chemical and microbial degradation studies.

Aerobic Soil Metabolism

In aerobic soil (the top layer of non-flooded soil), the non-linear parent, MIMPTS, and MPTS half-lives were 1.5, 32, and 53 days, respectively. The linear half-life of MPTS was 173 days. PTSOA did not exceed 0.7 % in the study (MRID 41765405).

Anaerobic Soil Metabolism

In the anaerobic soil metabolism study (flooded top layer of soil or the second layer of soil), the half-lives of parent DIMTS were 1.7 and 4.2 days in aerobic (non-flooded) and anaerobic (flooded soil) portions of the study, respectively. DIMTS was found in equal portions in water and sediment. MIMPTS was a major degradate with a half-life of 21 days and was found predominantly in water. MPTS reached 81 % by the end of the study and was primarily found in water (MRID 41765406).

Soil Photolysis

Soil photolysis half-lives of 13 days (linear) and 5.3 days (non-linear) were observed for parent compound. MIMPTS was stable in the dark control but degraded with a half-life of 12.5 day in irradiated sample. Volatiles and non-extractables were negligible (MRID 47323601).

Fate and Transport in WWTP

Activated Sludge Sorption Isotherm

Data have not been submitted for activated sludge sorption isotherm (ASSI) for DIMTS but it is not required. The log P for DIMTS is 2.66 (<3), and according to the Final 158W Rule, ASSI

data are not required if the log Kow is <3 (Testnote 19 of Environmental Fate Requirements Table).

Activated Sludge Biodegradation

In a ready biodegradability study (MRID 47338401, OECD 301F), DIMTS was not readily biodegradable at 28 and 67 mg/L because <60 % degraded within a 10-day window after 10 % degradation in the 28-day study. For the 67 mg/L test concentration, the amount of degradation by 10 days after 10 % degradation was 35-45 % % (28 mg/L data not provided). Degradate identification was not conducted in this study. On the other hand, the reference compound, sodium benzoate, was readily biodegradable because >60 % degraded in a 10-day window after 10 % degradation in the 28-day study.

In another ready biodegradability study (MRID 47024601, OECD 301B), DIMTS was readily biodegradable because >60 % degraded within a 10-day period after 10 % degradation occurred. In fact, DIMTS reached non-detectable concentrations by two days in the study. However, it was only primarily biodegradable and not ultimately biodegradable at 0.05 and 0.5 mg/L because the test material primarily formed terminal degradates other than CO_2 and water. For DIMTS residues, limited mineralization to CO_2 and water (11-14 %) was observed in the study. The degradate MIMPTS (parent minus one iodine) was readily biodegradable at 0.05 mg/L but not at 0.5 mg/L. The half-lives of the degradate MIMPTS (parent minus one iodine) were 1.2 day at 0.05 mg/L and 12.6 days at 0.5 mg/L, indicating that biodegradation is highly dependent on concentration. At 0.05 mg/L, MIMPTS declined to non-significant (<10 % of applied parent) concentrations by 7 days and was non-detectable by 21 days. At 0.5 mg/L, MIMPTS declined to 15.2 % by study termination (29 days). The terminal degradate MPTS accumulated and reached 81-96 % of applied at 0.05 mg/L and 74 % at 0.5 mg/L by study termination. The recoveries at 0.05 mg/L were 98.5 $\pm$ 5.5 %, and for 0.5 mg/L, were 112.4 $\pm$ 4.7 %. The reference compound (sodium benzoate) degraded completely and was both readily biodegradable and ultimately biodegradable

In a Zahn-Wellens study (OECD 302B, OCSPP 835.3200), the biodegradation of the degradate methyl-p-tolyl sulfone (MPTS) was studied at 5 and 75 mg/L. Inherent biodegradation (including primary and ultimate) was measured. The reference compound (aniline) was ultimately biodegradable based on the fact that 90 % of DOC was removed in four days, which is more than 70 % in 28 days. MPTS was not ultimately biodegradable because only about 48 % of DOC was removed in 28 days (MRID 47375909).

Activated Sludge Respiration Inhibition (ASRI)

DIMTS is not toxic to WWTP organisms when tested at >4.5 times its water solubility of <2 mg/L (Table 4). In other words, based on results from an ASRI test, DIMTS was not observed to inhibit activated sludge microorganisms at test concentrations as high as 9 mg/L. The results of the positive controls were within 15 % of each other and the IC_{50} value for the reference substance (sodium benzoate) was 12 mg/l, which is in the acceptable range of 5-30 mg/l (MRID 47373803). DIMTS would not be expected to reach concentrations as high as 9 mg/L based on its solubility of <2 mg/L. Consequently, no further ASRI testing is needed for DIMTS or its degradates.

Table B1. Environmental Fate Data Requirements for Diiodomethyl p-tolyl sulfone

Data Requirement (OCSPP guideline unless specified)	Study result	Degradate results	Reference (MRID unless specified) Status
Hydrolysis (835.2120)	Stable at pH 5 Half-lives of 2.1days at pH 7 and 3.6 days at pH 9	MIMPTS reached 90-100 % (end of study, 30 days) MPTS and PTSOA were minor degradates	43008701 Acceptable
Photodegradation in Water (835.2240)	Half-life of 1.4 hours	PTSOA (90 %) and MPTS (10 %) Stable in dark control	47343001 Acceptable
Photodegradation on Soil (835.2410)	Half-life of 5.3 days	MIMPTS half-life of 12.5 days (irradiated) Stable in dark controls	47323601 Acceptable
Aerobic Soil Metabolism (835.4100)	Half-life of 1.5 day	MIMPTS (32 days) MPTS (53 days)	41765405 Acceptable
Anaerobic Soil Metabolism (835.4200)	Half-life of 1.7 day (aerobic phase) Half-life of 4.2 days (anaerobic phase)	MIMPTS half-life of 21 days MPTS reached 81 % by the end of the study and did not decline.	41765406 Acceptable
Anaerobic Aquatic Metabolism (835.4400)	Half-life of 9.6 days	MIMPTS half-life of 11 days MPTS reached 95 % by end of study (180 days)	42177201 Acceptable
Aerobic Aquatic Metabolism (835.4300)	No data	N/A	Required
Leaching-Adsorption-Desorption (835.1230)	No data	No data	Required for DIMTS, MIMPTS, and MPTS
Bioaccumulation in Fish (850.1730)	No data	N/A	Not required because log P <3 for parent and degradates
Special Leaching Study (AWPA E11-06)	**Leaching rates** **5.6 mg/cm^3 trt rate (1 % w/w)** 23.5 (max) 19.1 (min) 20.4 (average) 19.9 (median) 309 (cumulative) 17.9 (% leached) **11.2 mg/cm^3 trt rate (2 % w/w)** 34.4 (max) 19.4 (min) 23.3 (average) 22.7 (median) 351 (cumulative) 9.9 (% leached) **16 mg/cm^3 trt rate (3 % w/w)**	N/A	47375907 Acceptable Max, min, average, and median leaching rates in µg/cm^2/day Cumulative leaching in µg/cm^2 Most relevant leaching rate is 5.6 mg/cm^3 treatment based on 1 % (w/w) treatment rate in study and 0.12-0.32 % AI treatment rate in Label Reg. No. 464-673

	49.3 (max) 21.1 (min) 25.8 (average) 23.5 (median) 413 (cumulative) 8.1 (% leached)		
Ready Biodegradability (835.3110)	DIMTS not readily biodegradable at 28 and 67 mg/L	Not measured	47338401 Acceptable OECD 301F
	DIMTS was primarily biodegradable at 0.05 and 0.5 mg/L Not detectable after 2 days	MIMPTS not detectable after 7 days in 0.05 mg/L DIMTS treatment MIMPTS detected throughout the 29-day study at 0.5 mg/L DIMTS treatment MIMPTS half-lives of 1.2 day at 0.05 mg/L and 12.6 days at 0.5 mg/L MPTS did not degrade in study	47024601 Supplemental OECD 301B
Inherent Biodegradability Zahn Wellens/EMPA Test (835.3200)	No data	MPTS (as parent compound) was not ultimately biodegradable at 5 and 75 mg/L	47375909 Acceptable
Inhibition of Sewage Sludge Respiration (850.3300)	Not inhibitory at >9 mg/L (4.5X water solubility based on Table 5)	N/A	47373803 Acceptable

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Appendix C Ecotoxicology Profile

Toxicity to Terrestrial Receptors

Birds

Based on studies in the agency's files, DIMTS appears to be practically nontoxic to birds when ingested on an acute or dietary basis. It is not anticipated that any further studies in birds will be required at this time.

C1 Birds (Acute Oral Toxicity & Dietary Toxicity)

Species	Chemical	% Active Ingredient	Endpoint	Toxicity Category	Satisfies Guidelines	MRID
Bobwhite quail *Colinus virginianus*)	Diiodomethyl p-tolyl sulfone **(Acute Oral)**	95	LD_{50} > 2000 (mg ai/kg bw)	Practically Non-Toxic	Yes (core)	123643
	Diiodomethyl p-tolyl sulfone **(Dietary)**	95	LD_{50} = 5620 (ppm)	Practically Non-Toxic	Yes (core)	123642
Mallard duck (*Anas platyrhynchos)*	Diiodomethyl p-tolyl sulfone **(Dietary)**	95	LD_{50} = 5620 (ppm)	Practically Non-Toxic	Yes (core)	124488

Mammals

Based on the results of mammalian studies conducted to meet human toxicity data requirements, diiodomethyl p-tolyl sulfone exhibits low acute oral and acute dermal toxicity (Toxicity Category IV), and high acute inhalation toxicity (Toxicity Category II). Diiodomethyl p-tolyl sulfone is classified as an eye corrosive (Toxicity Category I). For dermal irritation, diiodomethyl p-tolyl sulfone is a low irritant (Toxicity Category IV) and is not classified as a dermal sensitizer. It is not anticipated that any further studies in mammals will be required to assess the ecological risk posed by DIMTS. For further data refer to Appendix A.

Beneficial Insects

Per 40 CFR 158W, a honeybee acute contact study is typically required for chemicals labeled for use as wood preservatives. It is anticipated that an acute toxicity study in honeybees will be required to assess the risk posed by DIMTS to insect pollinators (see Guideline 850.3020).

Terrestrial Plants

Terrestrial plants are not expected to have significant exposure to DIMTS when used as directed. It is not anticipated that any studies in terrestrial plants will be required at this time.

Toxicity to Aquatic Receptors

Freshwater Fish

The agency requires higher tier testing based on a chemical's properties and fate in the environment.

Diiodomethyl p-tolyl sulfone is acutely toxic to freshwater organisms and forms soluble and persistent major degradates. As such, chronic toxicity data is required to gain a more complete understanding of the chemical's toxicity in aquatic environments. The requirement for chronic toxicity data in freshwater fish will be satisfied by a fish early-life stage study (see Guidelines 850.1400). Because DIMTS is highly susceptible to reductive dehalogenation in aqueous solution, the preferred experimental test substance is the major degradate, MIMPTS (parent minus one iodo group) degradate. The preferred freshwater test species is rainbow trout. This data is anticipated to be required.

C2 Freshwater Fish and Amphibian Toxicity Data

Species	Chemical	% Active Ingredient	Endpoint	Toxicity Category	Satisfies Guidelines	MRID
Rainbow trout *Oncorhynchus mykiss*)	Diiodomethyl p-tolyl sulfone	97.7%	96-h LC_{50} = 66.7 (µg ai/L)	Very highly toxic	Supplemen-tal	47234001
	Diiodomethyl p-tolyl sulfone	95%	96-h LC_{50} = 130 (µg ai/L)	Highly toxic	Yes (core)	149730
Bluegill sunfish *Lepomis macrochirus*)	Diiodomethyl p-tolyl sulfone	95%	96-h LC_{50} = 750 (µg ai/L)	Highly toxic	Yes (core)	149731

Freshwater Invertebrates

The agency requires higher tier testing based on a chemical's properties and fate in the environment.

Diiodomethyl p-tolyl sulfone is acutely toxic to freshwater organisms and forms soluble and persistent major degradates. As such, chronic toxicity data is required to gain a more complete understanding of the chemical's toxicity in aquatic environments. The requirement for chronic toxicity data in freshwater invertebrates will be satisfied by an aquatic invertebrate life-cycle study (see Guidelines 850.1300). Because DIMTS is highly susceptible to reductive dehalogenation in aqueous solution, the preferred experimental test substance is the major degradate, MIMPTS (parent minus one iodo group) degradate. The preferred freshwater test species is Daphnia magna. This data is anticipated to be required.

C3 Freshwater Invertebrates Toxicity Data

Species	Chemical	% Active Ingredient	Endpoint	Toxicity Category	Satisfies Guidelines	MRID
	Diiodomethyl p- tolyl sulfone	97.7%	48-h EC_{50} = 279 (µg ai/L)	Highly toxic	Yes (core)	47234002

Waterflea *(Daphnia magna)*	Diiodomethyl p- tolyl sulfone	95%	48-h EC_{50} = 7,400 (µg ai/L)[4]	Moderately Toxic	Yes (core)	149729
	Diiodomethyl p- tolyl sulfone	95%	48-h EC_{50} = 71 (µg ai/L)[5]	Very Highly Toxic	Supplemen-tal	123644

Estuarine/Marine Fish

Acute toxicity testing with estuarine/marine organisms using the TGAI is required when an end-use product is intended for direct application to the marine/estuarine environment or the active ingredient is expected to reach this environment in significant concentrations because of its expected use and mobility. As such, the agency requires acute toxicity data in estuarine/marine fish for DIMTS (see Guideline 850.1075). There are currently no acute toxicity data for diiodomethyl p-tolyl sulfone in estuarine/marine fish. This data is anticipated to be required.

Estuarine/Marine Invertebrates

Acute toxicity testing in estuarine marine organisms using the TGAI is required when an end-use product is intended for direct application to the marine/estuarine environment, or the active ingredient may reach the aquatic environment in significant concentrations as a result of leaching and environmental mobility, as in the use of DIMTS as a wood preservative. There are currently no acceptable acute toxicity data for estuarine/marine shrimp (see Guideline 850.1035), or estuarine/marine mollusk (see Guideline 850.1025) for diiodomethyl p-tolyl sulfone. This data is anticipated to be required.

Aquatic Plants

Microphytes and Floating Vascular Macrophytes

Acute toxicity testing in aquatic plants is required when an end-use product is intended for direct application to the marine/estuarine environment, or the active ingredient may reach the aquatic environment in significant concentrations as a result of leaching and environmental mobility, as in the use of DIMTS as a wood preservative. There are currently no acceptable toxicity data for diiodomethyl p-tolyl sulfone in vascular aquatic plants (see Guideline 850.4400), green algae (see Guideline 850.4500), or cyanobacteria (see Guideline 850.4550). This data is anticipated to be required.

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Appendix D Screening Level Down-the-Drain Analysis

The Down-the-Drain (DtD) module of E-FAST (Exposure and Fate Assessment Screening Tool), [version 2] was used to screen for the potential for aquatic organisms downstream of domestic wastewater treatment plants to be exposed to DIMTS and its degradates. The Down-the-Drain module uses daily per capita release of household wastewaters, stream dilution factors, and wastewater treatment plant removal efficiency to provide both high-end and median (average) time-averaged surface water concentrations of chemicals discharged by domestic wastewater treatment plants. The high-end scenario uses surface water concentrations downstream of domestic wastewater treatment plants based on the 10^{th} percentile stream dilution factor (SDF); the average scenario uses surface water concentrations based on the 50^{th} percentile SDF. SDF is defined as the ratio of the stream flow downstream of a wastewater treatment plant to the wastewater treatment plant flow. Inputs used to run the DtD module included concentrations of concern (COCs) for aquatic organisms, percent removal during wastewater treatment, and hypothetical wastewater treatment plant influent volumes.

The results of the DtD module are expressed as number of days of exceedance of COCs for aquatic organisms. COCs are grouped into 3 categories: acute, endangered/listed, and chronic. Acute COCs for freshwater fish and invertebrates were derived by dividing LC_{50} values for freshwater organisms by 2. Endangered/listed COCs for freshwater fish and invertebrates were derived by dividing LC_{50} values by 20. EC_{50} values for plants were used to establish acute COCs for plants. NOAEC values for plants were used to establish endangered/listed COCs for plants. Chronic COCs for freshwater fish and invertebrates are based on NOAEC values. For acute and endangered listed COCs, there may be potential concern for freshwater organisms if the COC is exceeded for 1 day or more. For chronic COCs, there may be potential concern for freshwater organisms if the COC is exceeded 20 days or more. In the absence of data on removal of DIMTS during wastewater treatment, no removal of DIMTS during wastewater treatment was assumed.

The Down-the-Drain module was first run using a high-end scenario to determine whether the model predicted exceedances of concentrations of concern. If the high-end scenario predicted exceedances of the concentration of concern, the model was also run using the average scenario.

Appendix E Product Chemistry

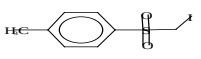
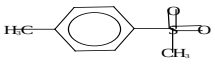
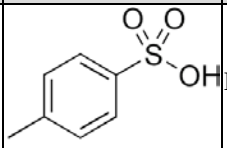
The product chemistry information for parent DIMTS relevant to risk assessment is summarized in Table E1, while the product chemistry information for the degradates monoiodo-p-methyltolylsulfone (MIMPTS, parent compound minus one iodo group), methyl-p- tolylsulfone (MPTS, parent compound minus both iodo groups) and p-toluene sulfonic acid (PTSOA, parent compound minus both iodo groups and a methyl group with added hydroxyl group) are summarized in Table E2.

Table E1 – Physical-Chemical and Environmental Fate Properties for Parent DIMTS

Guideline No.	Parameter	DIMTS	Reference (MRID unless specified) Comments
830.7050	UV/Visible Absorption	Max sorption at 288 nm, some tailing through 409 nm	47234003
830.7370	Dissociation constant (pKa)	Not applicable	48511201
830.7550	Octanol-water partition coefficient at 25 °C (Log K_{ow})	2.66	42177202
830.7840	Solubility in water (mg/L)	<2	47373801
830.7950	Vapor pressure (mmHg)	4.9×10^{-7}	47373801
None	Henry's law constant at 25 °C (atm-m^3/mol)	1.4×10^{-7}	Calculated

atm-m^3/mol = atmosphere cubic meter per mole; °C = degrees Celsius; mg/L = milligrams per liter; mmHg = millimeters of mercury;

Table E2 – Physical-Chemical and Environmental Fate Properties for Monoiodo-p-methyltolylsulfone (MIMPTS), methyl-p- tolylsulfone (MPTS), and p-toluene sulfonic acid (PTSOA) Degradates

Guideline No.	Parameter	Monoiodo-p-methyltolylsulfone (MIMPTS)	Methyl-p-tolyl sulfone (MPTS)	P-toluene sulfonic acid (PTSOA)	Reference (MRID unless specified) Comments
None	Structure				None
None	Description	Parent minus 1 iodine	Parent minus two iodines	Hydroxylated, once-demethylated MPTS	None
None	PC Code	None	None	None	Not applicable
None	CAS No.	37891-96-6	59203-01-9	104-15-4	Dow MSDS (MIMPTS)

Guideline No.	Parameter	Monoiodo-p-methyltolylsulfone (MIMPTS)	Methyl-p-tolyl sulfone (MPTS)	P-toluene sulfonic acid (PTSOA)	Reference (MRID unless specified) Comments
					Chemical Book (MPTS)
None	Smiles code	O=S(=O)(c(ccc(c1)C)c1)C(I)	O=S(=O)(c(ccc(c1)C)c1)C	O=S(O)(=O)(c(ccc(c1)C)c1)	EPI-WEB 4.11
None	Molecular formula	$C_8H_9IO_2S$	$C_8H_{10}O_2S$	$C_7H_8O_3S$	EPI-Web 4.11
None	Molecular weight	296.12	170.23	172.20	EPI-WEB 4.11
830.7050	UV/Visible Absorption	No data	No data	No data	Similar to parent
830.7370	Dissociation constant (pKa)	Not applicable	Not applicable	Not applicable	Similar to parent
830.7550	Octanol-water partition coefficient at 25 °C (Log K_{ow})	2.3	1.94	-0.62	47338402 (MIMPTS and MPTS) EPI-WEB 4.11 (PTSOA)
830.7840	Solubility in water (mg/L)	140.4	1,352	6.2×10^5	47338402 (MIMPTS and MPTS) EPI-WEB 4.11 (PTSOA)
830.7950	Vapor pressure (mmHg)	2.3×10^{-5}	2×10^{-3}	2.9×10^{-6}	EPI-WEB 4.11
None	Henry's law constant at 25 °C (atm-m^3/mol)	6.4×10^{-8}	3.3×10^{-7}	1.1×10^{-12}	Calculated

atm-m^3/mol = atmosphere cubic meter per mole; °C = degrees Celsius; mg/L = milligrams per liter; mmHg = millimeters of mercury.

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